



**COMPOUNDS USEFUL AS MODULATORS OF MELANOCORTIN  
RECEPTORS AND PHARMACEUTICAL COMPOSITIONS COMPRISING  
SAME**

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**Related Inventions**

This application claims the benefit of priority of US applications Serial Nos. 60/273,206, and 60/273,291, filed March 2, 2001, the entire contents of which are incorporated herein by reference.

**Field of the Invention**

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The present invention relates to compounds useful in treating diseases responsive to modulation of melanocortin receptors, to methods of treating such diseases, and to pharmaceutical compositions comprising same.

**Background of the Invention**

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Melanocortin peptides, particularly  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH), have a wide range of effects on biological functions including feeding behavior, pigmentation, and exocrine function. *See Wikberg et al., "New Aspects on the Melanocortins and their Receptors," Pharmacological Research*, Vol. 42, No. 5 (2000), at pp. 393-420. The biological effects of  $\alpha$ -MSH are mediated by a sub-family of G protein-coupled receptors, termed melanocortin receptors. *See Wikberg et al., supra*. There are  
20 four melanocortin receptors: MC-1R, MC-3R, MC-4R, and MC-5R (MC-2R is not a receptor for  $\alpha$ -MSH but is the adrenocorticotrophic hormone {ACTH} receptor). Activating any one of these receptors results in stimulation of cAMP formation.

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MC-1R was first found in melanocytes. Naturally occurring inactive variants of MC-1R in animals were shown to lead to alterations in pigmentation and a subsequent lighter coat color. From these and other studies, it is evident that MC-1R is an important regulator of melanin production and coat color in animals (or skin color in humans). MC-3R is expressed in the brain and peripheral tissues, and knock-out studies have revealed that MC-3R is responsible for alterations in feeding behavior and body weight. MC-4R is

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primarily expressed in the brain. Genetic knock-outs and pharmacologic manipulation of MC-4R in animals have shown that agonizing MC-4R causes weight loss and antagonizing MC-4R produces weight gain. MC-5R is ubiquitously expressed in many peripheral tissues and in the brain, but its expression is greatest in exocrine glands.

- 5 Genetic knock-out of this receptor in mice results in altered regulation of exocrine gland function, leading to changes in water repulsion and thermoregulation.

Much attention has been focused on the study of MC-3R and MC-4R modulators and their use in treating body weight disorders, such as obesity and anorexia. For example, WO 00/74679 to Merck & Co., Inc., “*Substituted Piperidines as Melanocortin-4-Receptor Agonists*,” (Dec. 14, 2000), and WO 99/64002 also to Merck & Co Inc., “*Spiropiperidine Derivatives as Melanocortin Receptor Agonists*,” (Dec. 16, 1999), disclose compounds that reportedly are selective agonists of MC-4R. Each of the compounds of WO 00/74679 and WO 99/64002 has a bicyclic terminal group, typically tetrahydroisoquinoline. Isoquinoline compounds, more particularly tetrahydro-  
 15 isoquinoline-based compounds, useful as melanocortin (MC) receptor agonists and antagonists are disclosed in US Pat. No. 6,127,381, “*Isoquinoline Compound Melanocortin Receptor Ligands and Method of Using Same*,” issued Oct. 3, 2000 to Basu *et al.* See also WO 01/91752, WO 01/70708, and WO 01/70337 to Merck and WO 02/00654 to Pfizer Products Inc., reportedly disclosing compounds for use as MC-4R  
 20 agonists. Individual compounds can bind to multiple MC receptors, with different levels of affinity. Yet it may be advantageous in treating diseases for compounds to be selective for one or more particular MC receptors. See, e.g., WO 00/58361 to Proctor & Gamble Co., “*Melanocortin Receptor Ligands*” (disclosing compounds that reportedly are selective for MC3R and MC4R in preference to MC-1R); and WO 99/54358 to Quadrant  
 25 Holdings Cambridge Ltd., “*Melanocortin Receptor Ligands*” (disclosing compounds that reportedly are selective for MC3R, MC4R and/or MC5R).

The melanocortin peptides have potent physiological effects besides their role in regulating pigmentation, feeding behavior, and exocrine function. In particular,  $\alpha$ -MSH has been shown to induce a potent anti-inflammatory effect in both acute and chronic

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models of inflammatory diseases including inflammatory bowel disease, renal ischemia/reperfusion injury, and endotoxin-induced hepatitis. *See Catania et al.*, “ *$\alpha$ -MSH in Normal Human Physiology and Disease States*,” Trends in Endocrinology and Metabolism, Vol. 11, No. 8 (2000) at pp. 304-308. Administration of  $\alpha$ -MSH (either i.p. or i.v.) in these models results in substantial lessening of inflammation-mediated tissue damage, a significant decrease in leukocyte infiltration, and a dramatic reduction in elevated levels of cytokines (*e.g.*, TNF- $\alpha$ ), chemokines (*e.g.*, MCP-1, IL-8), and inflammatory mediators (*e.g.*, i-NOS and ICAM-1), to near baseline levels. Earlier studies had shown that  $\alpha$ -MSH acts as an “anti-cytokine” in many acute inflammatory models, in effect antagonizing the pro-inflammatory actions of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6.

The anti-inflammatory actions of  $\alpha$ -MSH are mediated by MC-1R. MC-1R is expressed in cells that are important regulators of the immune response: monocyte/macrophages, neutrophils, endothelial, and mast cells. *See Catania et al.*, cited above. Stimulation with  $\alpha$ -MSH results in a dampening of the inflammatory response in these cells, including inhibition of nitric oxide formation, decreased expression of co-stimulatory molecules and adhesion receptors, and importantly, an increase in the expression of IL-10, a cytokine with potent anti-inflammatory actions. Studies have shown that MC-1R selective peptides are as efficacious as  $\alpha$ -MSH in eliciting an anti-inflammatory response. *See Wikberg*, “*Melanocortin Receptors: Perspectives for Novel Drugs*,” European Journal of Pharmacology, Vol. 375 (1999), at pp. 295-310, and WO 99/57148 to WA Pharma AB (1999), “*Melanocortin 1 Receptor Selective Compounds*.”

The mechanism by which agonism of MC-1R results in an anti-inflammatory response is likely through inhibition of the pro-inflammatory transcription activator, NF- $\kappa$ B. NF- $\kappa$ B is a pivotal component of the pro-inflammatory cascade, and its activation is a central event in initiating many inflammatory diseases. In a typical inflammatory response, NF- $\kappa$ B is activated in response to an inflammatory stimulus and once activated, induces expression of a wide array of pro-inflammatory genes. *See Tak and Firestein*, “*NF- $\kappa$ B: a Key Role in Inflammatory Diseases*,” The Journal of Clinical Investigation,

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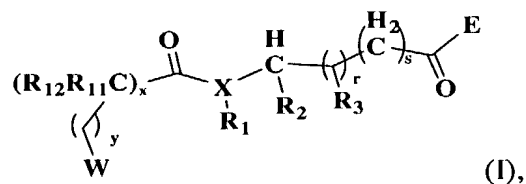
Vol. 107 (2001), pp. 7-11. Activation of MC-1R, and subsequent generation of cAMP and/or decreased production of nitric oxide, has been shown to inhibit activation of NF- $\kappa$ B. See Manna and Aggarwal, " *$\alpha$ -MSH Inhibits the Nuclear Transcription factor NF- $\kappa$ B Activation Induced by Various Inflammatory Agents,*" The Journal of Immunology, Vol. 161 (1998), pp. 2873-2880. Thus,  $\alpha$ -MSH exerts anti-inflammatory actions through stimulation of MC-1R on cells involved in the inflammatory response and subsequent inhibition of the activation of the pro-inflammatory transcription factor NF- $\kappa$ B. Additionally, studies show that anti-inflammatory actions of  $\alpha$ -MSH may be, in part, mediated by agonism of MC-3R and/or MC-5R. See WO 00/05263 to William Harvey Research Limited (2000), "*Compounds for Use in the Treatment of Inflammation.*"

The present invention provides compounds useful as modulators of the melanocortin receptors, including selective modulators of MC-1R and/or MC-4R. Compounds that reportedly are selective agonists of MC-1R are disclosed in WO 99/57148, cited above, and selective antagonists of MC-1R are disclosed in WO 99/43709 to The Regents of the Univ. of Calif., "*Melanocortin Receptor Antagonists and Modulations of Melanocortin Receptor Activity.*" Both WO 99/57148 and WO 99/43709 disclose large polypeptides. Small molecule inhibitors are advantageous in comparison to large polypeptides as they are less likely to induce immune reactions in patients and are more amenable to oral delivery. There remains a need for a small molecule useful as an MC-1R agonist, which is provided by the present invention. Melanocortin receptor modulators are also disclosed in US patent application Serial No. \_\_\_\_\_, filed concomitantly herewith by the same inventors herein and assigned to the present assignee, claiming priority to US patent applications Serial Nos. 60/273,206, and 60/273,291, filed March 2, 2001, the entire contents of which is incorporated herein by reference. Also incorporated herein is WO 99/58501 to Novo Nordisk.

### **Summary of the Invention**

The present invention is directed to compounds having the formula (I), useful as modulators of one or more melanocortin receptors,

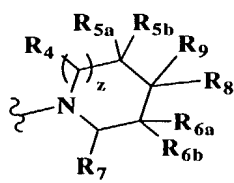
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and pharmaceutically-acceptable salts, hydrates or prodrugs thereof,

in which

in which



E is ;

X is N or CH;

R<sub>1</sub> is hydrogen or C<sub>1-6</sub>alkyl or is taken together with R<sub>2</sub> or R<sub>3</sub> to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R<sub>2</sub> is hydrogen, aryl, cycloalkyl, heteroaryl, heterocyclo; or C<sub>1-6</sub>alkyl or C<sub>2-6</sub>alkenyl optionally substituted with one to three of hydroxy, alkoxy, halogen, cyano, nitro, trifluoromethyl, amino, alkylamino, aryl, cycloalkyl, heteroaryl, and/or heterocyclo; or R<sub>2</sub> is taken together with R<sub>1</sub> or R<sub>3</sub> to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R<sub>3</sub> is hydrogen or C<sub>1-6</sub>alkyl or is taken together with R<sub>1</sub> or R<sub>2</sub> to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

R<sub>4</sub>, R<sub>5</sub>, R<sub>5a</sub>, R<sub>5b</sub>, R<sub>6</sub>, R<sub>6a</sub>, R<sub>6b</sub>, and R<sub>7</sub> are independently selected from hydrogen, alkyl, substituted alkyl, halogen, hydroxy, alkoxy, keto, aryl, heteroaryl, cycloalkyl, and heterocyclo, or R<sub>5a</sub> and/or R<sub>5b</sub>, R<sub>6a</sub> and/or R<sub>6b</sub>, are taken together with R<sub>8</sub> or R<sub>9</sub> to form a fused carbocyclic, heterocyclic or heteroaryl ring;

R<sub>8</sub> and R<sub>9</sub> are independently hydrogen, halogen, cyano, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclo, aryl, heteroaryl, -OR<sub>13</sub>, -NR<sub>13</sub>R<sub>14</sub>, -SR<sub>13</sub>

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$-S(O)_pR_{14}$ ,  $-C(=O)R_{13}$ ,  $-OC(=O)R_{13}$ ,  $-CO_2R_{13}$ ,  $-C(=O)NR_{13}R_{14}$ ,  $-NR_{13}C(=O)R_{14}$ ,  
 $-OC(=O)NR_{13}R_{14}$ ,  $-NR_{13}CO_2R_{14}$ ,  $-NR_{13}C(=O)NR_{14}R_{15}$  or  $-NR_{13}SO_2R_{14}$ ; or  $R_8$  and  
 $R_9$  taken together form a monocyclic or bicyclic cycloalkyl or heterocyclo joined  
in a spiro fashion to ring E at C\*, provided that  $R_8$  and  $R_9$  are not both hydrogen,  
5 and provided further that when  $R_8$  is  $-OR_{13}$ ,  $-(CH_2)_k$ -aryl or  $-(CH_2)_k$ -heteroaryl,  
then  $R_9$  is not  $-C(=O)NR_{18}R_{19}$ ,  $-CO_2R_{19}$ ,  $-(CH_2)_mNR_{18}SO_2R_{20}$ ,  
 $-(CH_2)_mNR_{18}C(=O)R_{20}$ ,  $-(CH_2)_mOR_{19}$ ,  $-(CH_2)_mO(C=O)R_{20}$ ,  $-CH(R_{18})R_{19}$ , or  
 $-(CH_2)_mNR_{18}(C=O)NR_{19}R_{21}$ ;

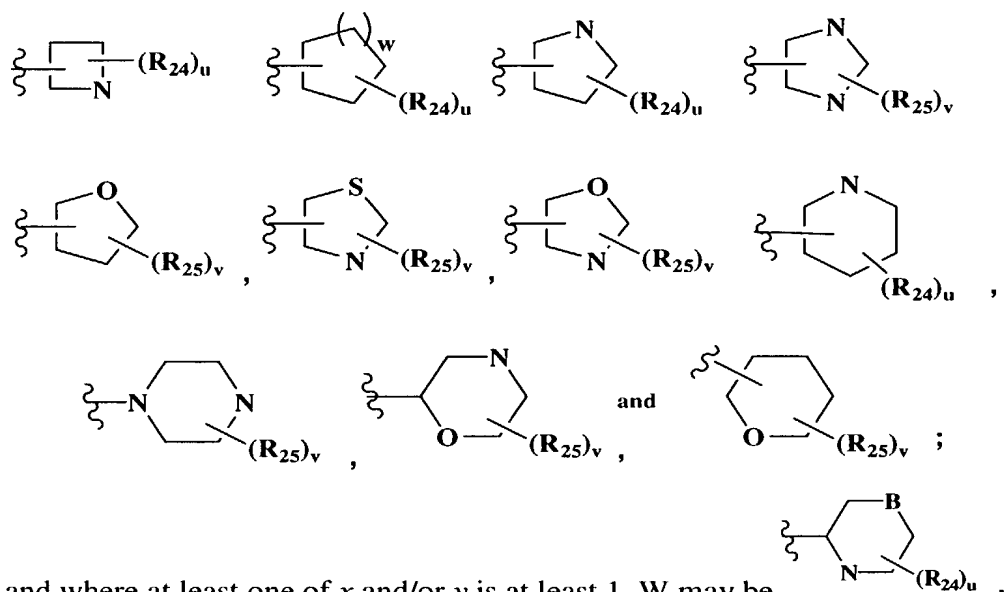
$R_{11}$  and  $R_{12}$  are selected independently of each other from hydrogen, alkyl, halogen,  
10 hydroxy, hydroxyalkyl, haloalkyl, amino, aminoalkyl, alkylamino, arylalkyl,  
cycloalkylalkyl, heteroarylalkyl, aryl, and cycloalkyl, and where  $y$  is at least 1,  
then  $R_{11}$  and  $R_{12}$  may be heterocyclo or heterocycloalkyl, or  $R_{11}$  and  $R_{12}$ , when  
attached to the same carbon atom, may join to form a spirocycloalkyl ring;

$R_{13}$ ,  $R_{14}$  and  $R_{15}$  are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl,  
15 heterocyclo, or heteroaryl; or  $R_{13}$  and  $R_{14}$ , or  $R_{14}$  and  $R_{15}$  may join together to  
form a heterocyclo or heteroaryl, except  $R_{14}$  is not hydrogen when joined to a  
sulfonyl group as in  $-S(O)_pR_{14}$  or  $-NR_{13}SO_2R_{14}$ ;

W is selected from:

- 1)  $-NR_{16}R_{17}$ ,  $-NR_{16}C(=O)R_{22}$ ,  $-NR_{16}CO_2R_{22}$ ,  $-OR_{23}$ , amidino, and guanidino;
- 20 2) heteroaryl or heterocyclo groups selected from pyrrolyl, furyl, thienyl,  
imidazolyl, pyrazolyl, isoxazolyl, thiazolyl, isothiazolyl, 3-azaisothiazolyl,  
pyridyl, pyrazinyl, pyridazinyl, 1,2-dihydropyridazinyl, and pyranyl, wherein said  
heteroaryl and heterocyclo groups may be substituted or unsubstituted and may  
have an optionally-substituted carbocyclic, heterocyclic or heteraryl ring fused  
25 thereto; or
- 3) a ring selected from:

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and where at least one of x and/or y is at least 1, W may be  
wherein B is N, O or S;

- 5  $R_{16}$  and  $R_{17}$  are selected from hydrogen, alkyl and substituted alkyl;  
 $R_{18}$ ,  $R_{19}$  and  $R_{21}$  are independently hydrogen or  $C_{1-6}$ alkyl optionally substituted with  
 halogen;  
 $R_{20}$  is  $C_{1-6}$ alkyl, aryl, or heteroaryl;  
 $R_{22}$  and  $R_{23}$  are independently selected from hydrogen, alkyl, substituted alkyl, aryl,
- 10 heteroaryl, cycloalkyl, and heterocyclo;
- $R_{24}$  and  $R_{25}$  at each occurrence are attached to any available carbon or nitrogen atom of W  
 and at each occurrence are selected from hydrogen,  $C_{1-6}$ alkyl, halogen, substituted  
 $C_{1-6}$ alkyl, amino, alkylamino, cyano, nitro, trifluoromethoxy,  $-C(=O)R_{26}$ ,  
 $-CO_2R_{26}$ ,  $-SO_2R_{26}$ ,  $-OR_{26}$ , aryl, heteroaryl, heterocyclo, and cycloalkyl, and/or
- 15 two  $R_{25}$  attached to two adjacent nitrogen or carbon atoms may join to form a  
 fused optionally-substituted heteroaryl, heterocyclo or cycloalkyl ring, and/or two  
 $R_{24}$  or two  $R_{25}$  when attached to the same carbon atom may form keto ( $=O$ );  
 $R_{26}$  is hydrogen, alkyl, substituted alkyl, aryl, heterocyclo, cycloalkyl, or heteroaryl,  
 except when joined to a sulphonyl group as in  $SO_2R_{26}$ , then  $R_{26}$  is not hydrogen;

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$k$  and  $m$  are independently 0, 1, 2 or 3;

$p$  is 1, 2, or 3;

$r$  is 0 or 1;

$s$  is 0 or 1;

5  $u$  and  $v$  are 0, 1, 2, or 3;

$w$  is 0, 1, or 2;

$x$  and  $y$  are 0, 1, 2, 3, or 4; and

$z$  is 0, 1, or 2.

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The invention is further directed to pharmaceutical compositions comprising one or more compounds according to formula (I). The invention is further directed to methods of treating melanocortin-receptor associated conditions, as defined herein, as well as methods of agonizing or antagonizing the melanocortin receptors, more particularly, MC-1R and MC-4R. The invention is also directed more generally to small molecule inhibitors of MC-1R, and to methods of treating diseases responsive to inhibition of MC-1R using a small molecule according to the invention.

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### **Detailed Description of the Invention**

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The following are definitions of terms used in this specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated.

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The term “alkyl” refers to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. Lower alkyl groups, that is, alkyl groups of 1 to 4 carbon atoms, are most preferred. When a subscript is used with reference to an alkyl or other group, the subscript refers to the number of carbon atoms that the group may contain.

The term “substituted alkyl” refers to an alkyl group as defined above having one, two or three substituents selected from the group consisting of halo, amino, cyano, keto



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(=O), -OR<sub>a</sub>, -SR<sub>a</sub>, NR<sub>a</sub>R<sub>b</sub>, -(C=O)R<sub>a</sub>, -CO<sub>2</sub>R<sub>a</sub>, -C(=O)NR<sub>a</sub>R<sub>b</sub>, -NR<sub>a</sub>C(=O)R<sub>b</sub>, NR<sub>a</sub>CO<sub>2</sub>R<sub>b</sub>, -OC(=O)R<sub>a</sub>, -OC(=O)NR<sub>a</sub>R<sub>b</sub>, -NR<sub>c</sub>C(=O)NR<sub>a</sub>R<sub>b</sub>, NR<sub>a</sub>SO<sub>2</sub>R<sub>d</sub>, SO<sub>2</sub>R<sub>d</sub>, SO<sub>3</sub>R<sub>d</sub>, cycloalkyl, aryl, heteroaryl, or heterocycle, wherein the groups R<sub>a</sub>, R<sub>b</sub>, and R<sub>c</sub> are selected from hydrogen, C<sub>1-6</sub>alkyl, aryl, heteroaryl, heterocycle, cycloalkyl, or C<sub>1-6</sub>alkyl substituted with  
5 halogen, hydroxy, methoxy, nitro, amino, cyano, -(C=O)H, -CO<sub>2</sub>H, -(C=O)alkyl, -CO<sub>2</sub>alkyl, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)<sub>2</sub>, carboxy, acyl, -C(=O)H, -C(=O)phenyl, -CO<sub>2</sub>-alkyl, cycloalkyl, -(C=O)NH<sub>2</sub>, -(C=O)NH(alkyl), -(C=O)NH(cycloalkyl), -(C=O)N(alkyl)<sub>2</sub>, -C(=O)-(CH<sub>2</sub>)<sub>1-2</sub>NH<sub>2</sub>, -C(=O)-(CH<sub>2</sub>)<sub>1-2</sub>NH(alkyl), -C(=O)-(CH<sub>2</sub>)<sub>1-2</sub>N(alkyl)<sub>2</sub>, -NH-CH<sub>2</sub>-carboxy, -NH-CH<sub>2</sub>-CO<sub>2</sub>-alkyl, phenyl,  
10 benzyl, phenylethyl, or phenyloxy. The group R<sub>d</sub> may be selected from the same groups as R<sub>a</sub>, R<sub>b</sub> and R<sub>c</sub> but is not hydrogen. Alternatively, the groups R<sub>a</sub> and R<sub>b</sub> may together form a heterocyclo or heteroaryl ring. It should be understood that when a substituted alkyl group is substituted with an aryl, cycloalkyl, heteroaryl, or heterocyclo, such rings are as defined below and thus may have one to three substituents as set forth below in the  
15 definitions for these terms.

When the term “alkyl” is used as a suffix following another specifically named group, *e.g.*, arylalkyl, heteroarylalkyl, the term defines with more specificity at least one of the substituents that the substituted alkyl will contain. For example, arylalkyl refers to an aryl bonded through an alkyl, or in other words, a substituted alkyl group having from  
20 1 to 12 carbon atoms and at least one substituent that is aryl (*e.g.*, benzyl or biphenyl). “Lower arylalkyl” refers to substituted alkyl groups having 1 to 4 carbon atoms and at least one aryl substituent.

The term “alkenyl” refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one double bond. Alkenyl groups of 2 to 6  
25 carbon atoms and having one double bond are most preferred.

The term “alkynyl” refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one triple bond. Alkynyl groups of 2 to 6 carbon atoms and having one triple bond are most preferred. A substituted alkenyl or alkynyl will contain one, two, or three substituents as defined above for alkyl groups.

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The term “alkylene” refers to bivalent straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms, *e.g.*,  $\{-\text{CH}_2-\}_n$ , wherein  $n$  is 1 to 12, preferably 1-8. Lower alkylene groups, that is, alkylene groups of 1 to 4 carbon atoms, are most preferred. The terms “alkenylene” and “alkynylene” refer to bivalent radicals of alkenyl and alkynyl groups, respectively, as defined above. Substituted alkylene, alkenylene, and alkynylene groups may have substituents as defined above for substituted alkyl groups.

The term “alkoxy” refers to the group  $\text{OR}_e$  wherein  $\text{R}_e$  is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heterocycle, or cycloalkyl. Thus, an alkoxy includes such groups as methoxy, ethoxy, cyclopropyloxy, pyrrolidinyloxy, and so forth. The term “aryloxy” refers to the groups  $\text{O}(\text{aryl})$  or  $\text{O}(\text{heteraryl})$ , wherein aryl and heteroaryl are as defined below.

The term “alkylthio” refers to an alkyl or substituted alkyl group as defined above bonded through one or more sulfur ( $-\text{S}-$ ) atoms, *e.g.*,  $-\text{S}(\text{alkyl})$  or  $-\text{S}(\text{alkyl}-\text{R}_a)$ .

The term “alkylamino” refers to an alkyl or substituted alkyl group as defined above bonded through one or more nitrogen ( $-\text{NR}_f-$ ) groups, wherein  $\text{R}_f$  is hydrogen, alkyl, substituted alkyl, or cycloalkyl.

The term “acyl” refers to an alkyl or substituted alkyl group as defined above bonded through one or more carbonyl  $\{-\text{C}(=\text{O})-\}$  groups. When the term acyl is used in conjunction with another group, as in acylamino, this refers to the carbonyl group  $\{-\text{C}(=\text{O})\}$  linked to the second named group. Thus, acylamino refers to  $-\text{C}(=\text{O})\text{NH}_2$ , substituted acylamino refers to the group  $-\text{C}(=\text{O})\text{NRR}$ , and acylaryl refers to  $-\text{C}(=\text{O})(\text{aryl})$ .

The term “aminoacyl” refers to the group  $-\text{NR}_f\text{C}(=\text{O})\text{R}_g$ , wherein  $\text{R}_g$  is hydrogen, alkyl, or substituted alkyl, and  $\text{R}_f$  is as defined above for alkylamino groups.

The term “halo” or “halogen” refers to chloro, bromo, fluoro and iodo.

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The term "carboxy" when used alone refers to the group  $\text{CO}_2\text{H}$ . Carboxyalkyl refers to the group  $\text{CO}_2\text{R}$ , wherein R is alkyl or substituted alkyl.

The term "sulphonyl" refers to a sulfoxide group (i.e.,  $-\text{S}(\text{O})_{1-2}-$ ) linked to an organic radical including an alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, or substituted alkynyl group, as defined above. The organic radical to which the sulfoxide group is attached may be monovalent (e.g.,  $-\text{SO}_2\text{-alkyl}$ ), or bivalent (e.g.,  $-\text{SO}_2\text{-alkylene}$ , etc.)

The term "amidino" refers to the group  $-\text{NR}_h-\overset{\text{NR}_i}{\underset{\parallel}{\text{C}}}-\text{R}_j$ , and the term "guanidino" refers to the group  $-\text{NR}_h-\overset{\text{NR}_i}{\underset{\parallel}{\text{C}}}-\text{NHR}_j$ , wherein for each of amidino and guanidino  $\text{R}_h$ ,  $\text{R}_i$ , and  $\text{R}_j$  may be hydrogen, alkyl, or substituted alkyl, or any two of  $\text{R}_h$ ,  $\text{R}_i$ , and  $\text{R}_j$  may join to form a heterocyclo or heteroaryl ring with the other of  $\text{R}_h$ ,  $\text{R}_i$ , and  $\text{R}_j$  comprising hydrogen, alkyl, or substituted alkyl.

The term "cycloalkyl" refers to substituted and unsubstituted monocyclic or bicyclic hydrocarbon groups of 3 to 9 carbon atoms which are, respectively, fully saturated or partially unsaturated, including a fused aryl ring, for example, an indan. A cycloalkyl group may be substituted by one or more (such as one to three) substituents selected from alkyl, substituted alkyl, aminoalkyl, halogen, cyano, nitro, trifluoromethyl, hydroxy, alkoxy, alkylamino, sulphonyl,  $-\text{SO}_2(\text{aryl})$ ,  $-\text{CO}_2\text{H}$ ,  $-\text{CO}_2\text{-alkyl}$ ,  $-\text{C}(=\text{O})\text{H}$ , keto,  $-\text{C}(=\text{O})-(\text{CH}_2)_{1-2}\text{NH}_2$ ,  $-\text{C}(=\text{O})-(\text{CH}_2)_{1-2}\text{NH}(\text{alkyl})$ ,  $-\text{C}(=\text{O})-(\text{CH}_2)_{1-2}\text{N}(\text{alkyl})_2$ , acyl, aryl, heterocycle, heteroaryl, or another cycloalkyl ring of 3 to 7 carbon atoms. The term "cycloalkylene" refers to a cycloalkyl forming a link or spacer between two other groups, i.e., a cycloalkylene is a cycloalkyl that is bonded to at least two other groups. The term cycloalkyl includes saturated or partially unsaturated carbocyclic rings having a carbon-carbon bridge of three to four carbon atoms or having a benzene ring joined thereto. When the cycloalkyl group is substituted with a further ring, said further ring may have one to two substituents selected from  $\text{R}_k$ , wherein  $\text{R}_k$  is lower alkyl, hydroxy, lower alkoxy, amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, nitro, and lower alkyl

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substituted with one to two hydroxy, lower alkoxy, amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, and/or nitro.

The term “aryl” refers to substituted and unsubstituted phenyl, 1-naphthyl and 2-naphthyl, with phenyl being preferred. The aryl may have zero, one, two or three  
 5 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, alkylthio, halo, hydroxy, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, sulphonyl, -SO<sub>2</sub>(aryl), -NH(alkyl), -NH(cycloalkyl), -N(alkyl)<sub>2</sub>, carboxy, acyl, -C(=O)H, -C(=O)phenyl, -CO<sub>2</sub>-alkyl, cycloalkyl, -(C=O)NH<sub>2</sub>, -(C=O)NH(alkyl), -(C=O)NH(cycloalkyl), -(C=O)N(alkyl)<sub>2</sub>, -NH-CH<sub>2</sub>-carboxy, -NH-CH<sub>2</sub>-CO<sub>2</sub>-alkyl, -  
 10 C(=O)-(CH<sub>2</sub>)<sub>1-2</sub>NH<sub>2</sub>, -C(=O)-(CH<sub>2</sub>)<sub>1-2</sub>NH(alkyl), -C(=O)-(CH<sub>2</sub>)<sub>1-2</sub>N(alkyl)<sub>2</sub>, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, heterocyclo, heteroaryl, or a C<sub>3-7</sub>cycloalkyl ring. The term “arylene” refers to an aryl as defined above forming a link or spacer between two other groups, *i.e.*, an arylene is an aryl that is bonded to at least two other groups. When the aryl group is substituted with a further ring, said further ring may have  
 15 one to two substituents selected from R<sub>k</sub>, wherein R<sub>k</sub> is defined as above.

The term “carbocyclo” or “carbocyclic” refers to a cyclic group in which all ring atoms are carbon, including optionally-substituted cycloalkyl and aryl groups, as defined herein.


The term “heterocyclo” or “heterocycle” refers to substituted and unsubstituted  
 20 non-aromatic 3 to 7 membered monocyclic groups, 7 to 11 membered bicyclic groups, and 10 to 15 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heterocyclo group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further  
 25 provided that the ring contains at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The heterocyclo group

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may be attached at any available nitrogen or carbon atom. The heterocyclo ring may contain one, two or three substituents selected from the group consisting of halo, amino, cyano, alkyl, substituted alkyl, trifluoromethyl, trifluoromethoxy, sulphonyl, -SO<sub>2</sub>(aryl), -NH(alkyl), -NH(cycloalkyl), -N(alkyl)<sub>2</sub>, alkoxy, alkylthio, hydroxy, nitro, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, carboxy, -CO<sub>2</sub>-alkyl, cycloalkyl, -C(=O)H, acyl, -

5 (C=O)NH<sub>2</sub>, -(C=O)NH(alkyl), -(C=O)NH(cycloalkyl), -(C=O)N(alkyl)<sub>2</sub>, -NH-CH<sub>2</sub>-carboxy, -NH-CH<sub>2</sub>-CO<sub>2</sub>-alkyl, -C(=O)-(CH<sub>2</sub>)<sub>1-2</sub>NH<sub>2</sub>, -C(=O)-(CH<sub>2</sub>)<sub>1-2</sub>NH(alkyl), -C(=O)-(CH<sub>2</sub>)<sub>1-2</sub>N(alkyl)<sub>2</sub>, heterocyclo, heteroaryl, a C<sub>3-7</sub>cycloalkyl ring. keto, =N-OH, =N-O-lower alkyl, or a five or six membered ketal, *i.e.*, 1,3-dioxolane or 1,3-dioxane. The

10 heterocyclo ring may have a sulfur heteroatom that is substituted with one or more

oxygen (=O) atoms, as for example, in . The term “heterocyclene” refers to a heterocycle as defined above forming a link or spacer between two other groups. When the heterocyclo group is substituted with a further ring, said further ring may have one to two substituents selected from R<sub>k</sub>, wherein R<sub>k</sub> is defined as above.

15 Exemplary monocyclic groups include azetidiny, pyrrolidiny, oxetany, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodiny, 2-oxoazepinyl, azepinyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-

20 dioxothienyl and the like. Exemplary bicyclic heterocyclo groups include quinuclidinyl.

The term “heteroaryl” refers to substituted and unsubstituted aromatic 5 or 6 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or


25 two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and

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sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any

5 ring. The heteroaryl ring system may contain one, two or three substituents selected from the group consisting of halo, amino, cyano, alkyl, substituted alkyl, trifluoromethyl, trifluoromethoxy, sulphonyl, -SO<sub>2</sub>(aryl), -NH(alkyl), -NH(cycloalkyl), -N(alkyl)<sub>2</sub>, alkoxy, alkylthio, hydroxy, nitro, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, carboxy, -CO<sub>2</sub>-alkyl, cycloalkyl, -C(=O)H, acyl, -(C=O)NH<sub>2</sub>, -(C=O)NH(alkyl), -

10 (C=O)NH(cycloalkyl), -(C=O)N(alkyl)<sub>2</sub>, -NH-CH<sub>2</sub>-carboxy, -NH-CH<sub>2</sub>-CO<sub>2</sub>-alkyl, -C(=O)-(CH<sub>2</sub>)<sub>1-2</sub>NH<sub>2</sub>, -C(=O)-(CH<sub>2</sub>)<sub>1-2</sub>NH(alkyl), -C(=O)-(CH<sub>2</sub>)<sub>1-2</sub>N(alkyl)<sub>2</sub>, heterocyclo, heteroaryl, or a C<sub>3-7</sub>cycloalkyl ring. The heterocyclo ring may have a sulfur heteroatom

that is substituted with one or more oxygen (=O) atoms, as for example, in . The term “heteroarylene” or “heterarylene” refers to a heteroaryl as defined above forming a

15 link or spacer between two other groups, *i.e.*, it is a heteroaryl that is bonded to at least two other groups. When the heteroaryl group is substituted with a further ring, said further ring may have one to two substituents selected from R<sub>k</sub>, wherein R<sub>k</sub> is defined as above.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl,

20 imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

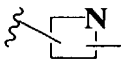
Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothieryl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl,

25 coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

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Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

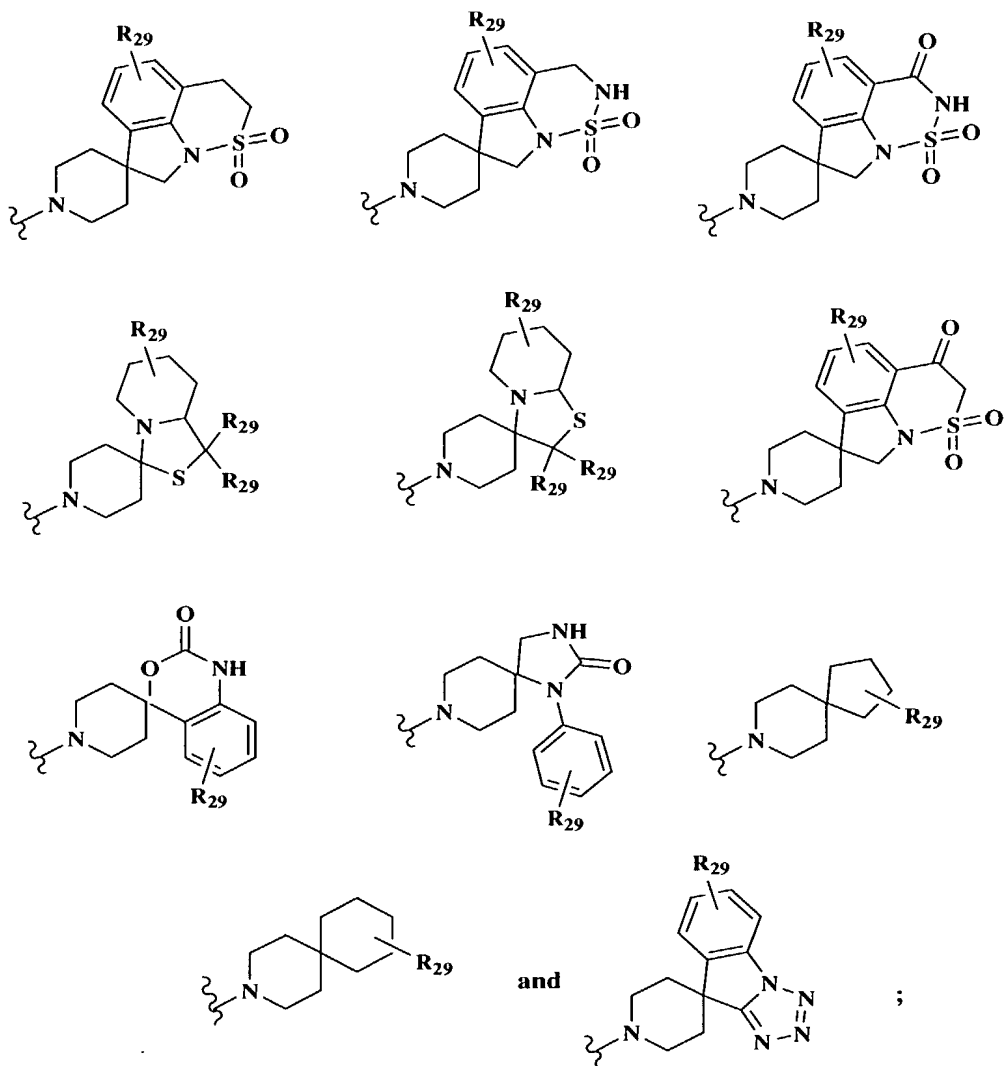
When reference is made herein to a particularly-named heterocyclic or heteroaryl group, such as azetidiny, imidazolyl, piperazinyl, and so forth, the named ring may optionally contain one or more (preferably one to three) substituents selected from the substituents recited above for heteroaryl and heterocyclo groups, as appropriate. The term azetidiny refers to an optionally-substituted four membered ring having one

nitrogen heteroatom, i.e., , wherein R can be any substituent defined herein for heterocyclo groups and unless otherwise stated, the azetidiny ring can be attached to another group at any available carbon atom or at the nitrogen atom.

When reference is made to a particularly-named group having at least one heterocyclo, heteroaryl, or carbocyclic ring “joined” thereto, it is meant that two substituents attached to the same, adjacent, or non-adjacent atoms of the particularly-named group may join to form a second or third ring (*i.e.*, the further ring may be fused, bridged or attached in a spiro fashion.) Each ring of these bicyclic or tricyclic groups may be optionally substituted, wherein the substituents are selected from those recited above for cycloalkyl, aryl, heterocyclo and heteroaryl groups. Thus, an imidazole having at least one ring joined thereto may include an aryl-fused imidazole such as benzimidazole having one or more (preferably one to three substituents), to an heteroaryl-fused imidazole such as a pyridoimidazole having one or more (preferably one to three) substituents, and so forth.

Accordingly, the above definitions and optional substituents for cycloalkyl, heterocyclo, and heteroaryl groups include spirocyclic ring systems. To illustrate, in compounds of formula (I) above, R<sub>8</sub> and R<sub>9</sub> are recited as optionally forming a spirocyclic ring. Thus, when z is 1, R<sub>8</sub> and R<sub>9</sub> together with the piperidine to which they are attached may be selected from the following exemplary groups, among others:

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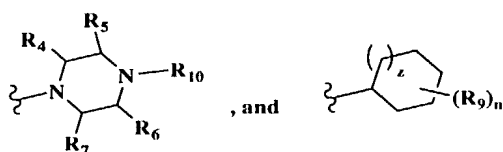


in which each  $R_{29}$  group is hydrogen or selected from the above-recited substituents for aryl, cycloalkyl, heterocyclo and heteroaryl groups.

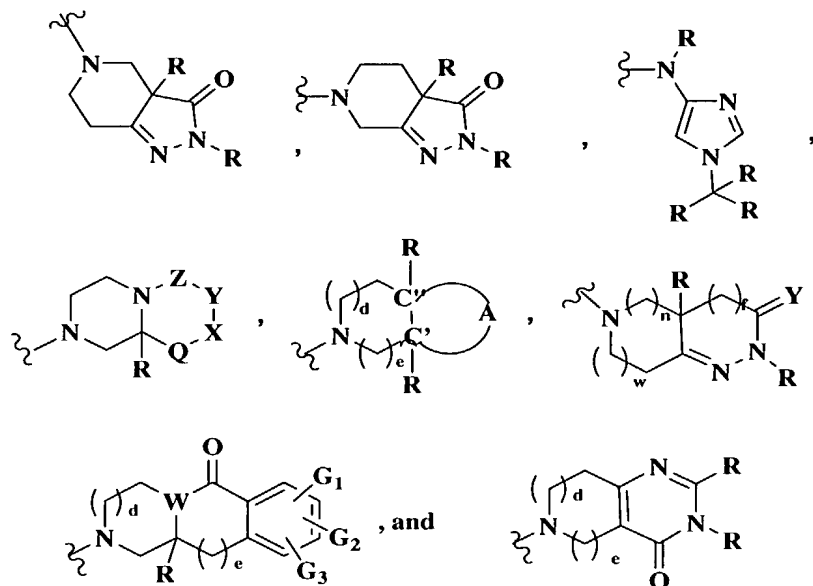
Additionally, one skilled in the field may make appropriate substitutions for the various groups of compounds of formula (I) herein, without departing from the spirit and scope of the invention. For example, it will be appreciated that in compounds of formula (I), the group E can be replaced with other groups, such as the groups  $E_2$ ,  $E_3$  and  $E_4$  shown in US application Serial No. , filed concomitantly herewith and incorporated herein, *i.e.*, groups having the formula,  $-NR_{11}R_{12}$ ,



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; wherein the various groups R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>,

R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, and R<sub>12</sub> are as defined in that application. Additionally, one may appreciate  
 5 that the group E as recited in compounds of formula (I) may be selected from, or replaced  
 with groups such as,



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as defined in WO 02/00654 and WO 01/91752, wherein the various groups R, A, G<sub>1-3</sub>, Q,  
 W, X, Y, Z, d, e, f, n and w, may be selected from groups recited in WO 02/00654 and/or  
 WO 01/91752, incorporated herein by reference.

Throughout the specification, groups and substituents thereof may be chosen to  
 15 provide stable moieties and compounds.

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The compounds of formula I form salts which are also within the scope of this invention. Reference to a compound of the formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of formula I contains both a basic moiety, such as, but not limited to an amine or a pyridine or imidazole ring, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, although other salts are also contemplated as within the scope of the invention, *e.g.*, they may be useful in isolation or purification steps which may be employed during preparation. Salts of the compounds of the formula I may be formed, for example, by reacting a compound of the formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

The compounds of formula I which contain a basic moiety, such as, but not limited to an amine or a pyridine or imidazole ring, may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotines, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

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The compounds of formula I which contain an acidic moiety, such as, but not limited to a carboxylic acid, may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts  
5 with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines [formed with N,N-bis(dehydroabietyl)ethylenediamine], N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (*e.g.*,  
10 methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.*, decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

Prodrugs and solvates of the compounds of this invention are also contemplated  
15 herein. The term "prodrug", as employed herein, denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula I, and/or a salt and/or solvate thereof. Solvates of the compounds of formula I are preferably hydrates.

Compounds of the formula I and salts thereof may exist in their tautomeric form  
20 (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers of the present compounds, such as those, for example, which may exist due to asymmetric carbons, including enantiomeric forms (which may exist even in the absence of asymmetric carbons) and diastereomeric forms, are contemplated  
25 and within the scope of this invention. Individual stereoisomers of the compounds of this invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other or other selected, stereoisomers. The chiral

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centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations.

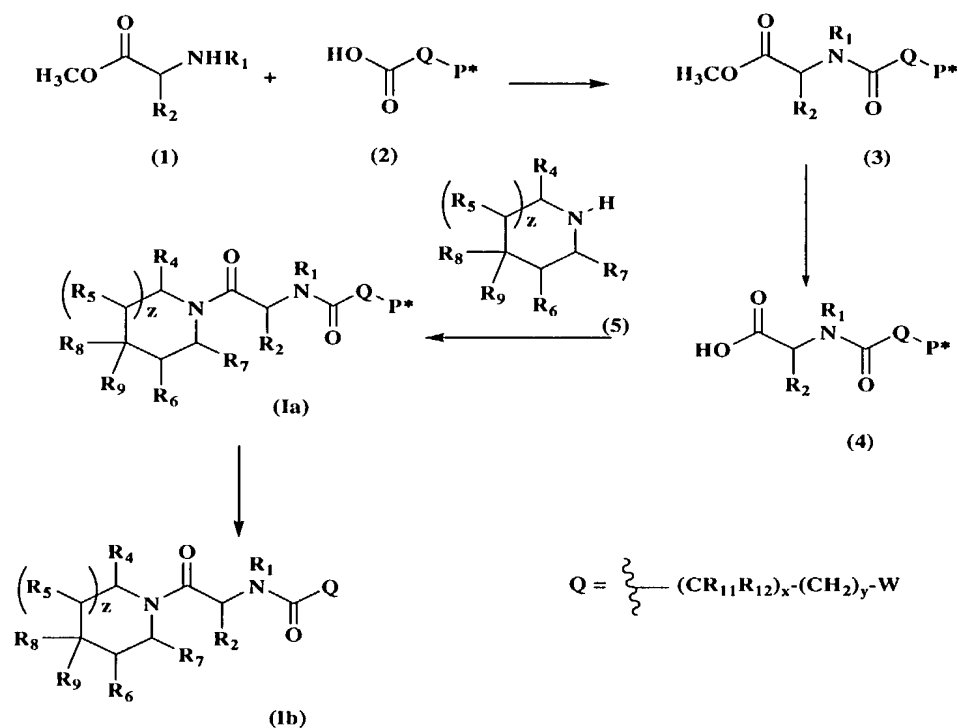
### **Methods of Preparation**

5           The compounds of the present invention may be prepared by methods such as those illustrated in the following Schemes I to III. Starting materials are commercially available or can be readily prepared by one of ordinary skill in the art using known methods. For all of the schemes and compounds, the designated groups such as E, W, R<sub>8</sub>, R<sub>9</sub>, etc., are as described above for a compound of formula I, unless otherwise indicated.

10           Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or readily prepared by one of ordinary skill in the art. High Speed Analoging (HSA) may be employed in the preparation of compounds, for example, where the intermediates possess a carboxylic acid or amino group.

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**Scheme I**

Compounds of formula (Ib) can be prepared from compounds (Ia) [wherein P\* is an amino protecting group, such as -Boc-, -CBZ-, -Fmoc-, which can be present in Q as in formula (Ia) or independently bonded to Q] via an appropriate amine deprotection process in an inert solvent at a temperature in the range -10°C to 100°C. The choice of deprotection routes can be chosen by one of ordinary skill in the art. They include, but are not limited to TFA or hydrogen chloride acid for -Boc-, hydrogenation with an appropriate metal catalyst (such as Pd), for -CBZ-, or a base, such as NMM or DEA, for -Fmoc-. Inert solvents include, but are not limited to methylene dichloride, alcoholic solvents, THF, acetic acid, DMF, acetonitrile, and dioxane.

Compounds of formula (Ia) can be prepared by the coupling of compounds of formula (5) with compounds (4) using an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary carboxylic acid activating agents include

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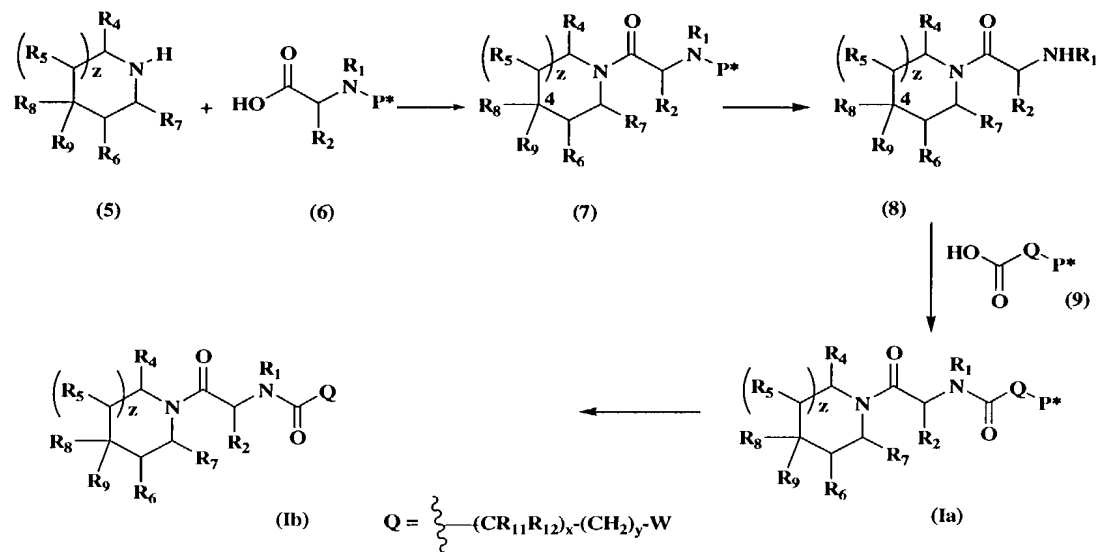
carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or other activating agents known by one of ordinary skill in the art. Exemplary inert solvents include ethers, including THF and dioxane, DMF, acetonitrile, or CH<sub>2</sub>Cl<sub>2</sub>.

- 5           Compounds (4) can be prepared by the hydrolysis of compounds (3) using a hydroxide source. Exemplary hydroxide sources include NaOH or LiOH. Exemplary solvents include water, alcohols, and mixtures of ethers/water.

- 10           Compounds (3) can be prepared by the coupling of compounds (1) and (2) using an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary carboxylic acid activating agents include carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or other activating agents known by one of ordinary skill in the art. Exemplary inert solvents include ethers, including THF and dioxane, DMF, acetonitrile, or CH<sub>2</sub>Cl<sub>2</sub>.

- 15           Compounds (1), (2) and (3) are either commercially available or available by methods known to one of ordinary skill in the art.

## **Scheme II**



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Compounds of formula (Ib) can be prepared from compounds of formula (Ia) [wherein P\* is an amino-protecting group as in Scheme I] via an appropriate amine deprotection process in an inert solvent at a temperature in the range from -10°C to 100°C.

5 The choice of deprotection routes can be chosen by one of ordinary skill in the art. They include, but are not limited to TFA or hydrogen chloride acid for -Boc-, hydrogenation with an appropriate metal catalyst for -CBZ-, or a base, such as NMM or DEA, for -Fmoc-. Inert solvents include, but are not limited to methylene dichloride, alcoholic solvents, THF, acetic acid, DMF, acetonitrile, and dioxane.

10 Compounds of formula (Ia) can be prepared by the coupling of compounds (8) and (9) using an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary carboxylic acid activating agents include carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or other activating agents known by one of  
15 ordinary skill in the art. Exemplary inert solvents include ethers, including THF and dioxane, DMF, acetonitrile, or CH<sub>2</sub>Cl<sub>2</sub>.

Compounds (8) [wherein P\* is an amino-protecting group as above] can be prepared from compounds (7) via an appropriate amine deprotection process in an inert solvent at temperatures ranging from -10°C to 100 °C. The choice of deprotection routes  
20 can be chosen by one of ordinary skill in the art and include those referenced above in Scheme I for -Boc-, -CBZ-, and -Fmoc-. Inert solvents include, but are not limited to methylene dichloride, alcoholic solvents, THF, acetic acid, DMF, acetonitrile, and dioxane.

Compounds (7) can be prepared by the coupling of compounds (5) and (6) using  
25 an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary carboxylic acid activating agents include carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol trifluoroacetate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or

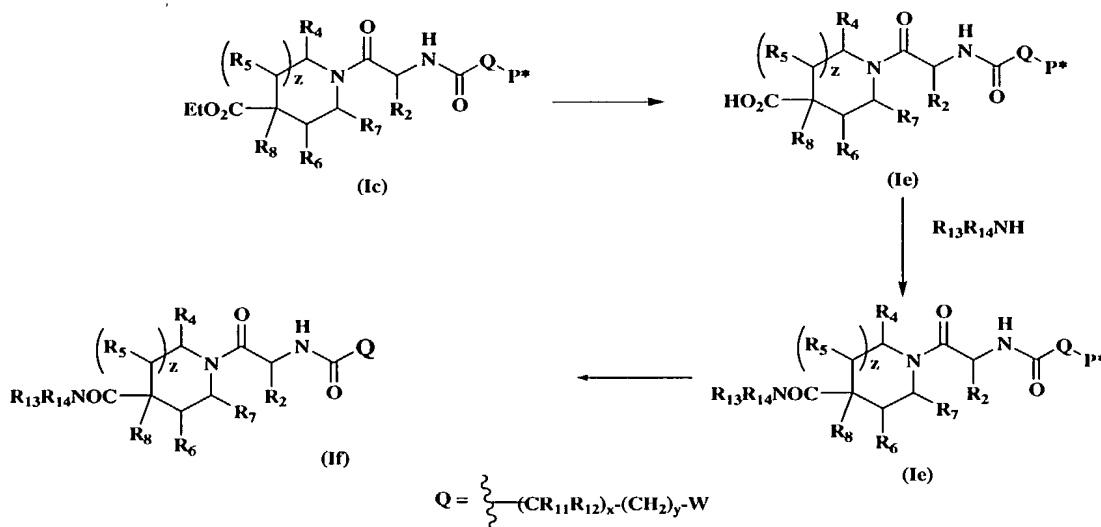
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other activating agents known by one of ordinary skill in the art. Exemplary inert solvents include ethers, including THF and dioxane, DMF, acetonitrile, or  $\text{CH}_2\text{Cl}_2$ .

Compounds (5) and (6) are either commercially available or available by methods known to one of ordinary skill in the art.

5

### Scheme III



10 Compounds of formula (If) can be prepared from compounds of formula (Ie) [wherein  $\text{P}^*$  is an amino protecting group as in Scheme I] via an appropriate amine deprotection process chosen by one of ordinary skill in the art, such as described above in Schemes I and II.

Compounds of formula (Ie) can be prepared by the coupling of compounds of  
 15 formula (Id) with amines of the formula  $\text{R}_{13}\text{R}_{14}\text{NH}$  using an appropriate carboxylic acid activating reagent in an inert solvent. Exemplary carboxylic acid activating agents include carbonyldiimidazole, dicyclohexylcarbodiimide, pentofluorophenol



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trifluoroacetate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, or other activating agents known by one of ordinary skill in the art. Exemplary inert solvents include ethers, including THF and dioxane, DMF, acetonitrile, or CH<sub>2</sub>Cl<sub>2</sub>.

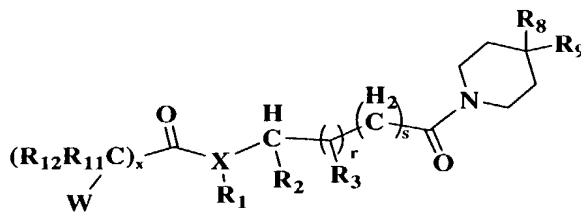
Compounds of formula (Id) can be prepared by the hydrolysis of compounds of formula (Ic) using a hydroxide source. Exemplary hydroxide sources include NaOH or LiOH. Exemplary solvents include water, alcohols, and mixtures of ethers/water.

Amines of the formula R<sub>13</sub>R<sub>14</sub>NH are either commercially available or available by methods known to one of ordinary skill in the art. Compounds of formula (Ic) can be prepared as described above in Schemes I and II.

All documents cited in the present specification are incorporated herein by reference in their entirety.

### Preferred Compounds

Preferred compounds are those according to formula (I) having the formula,



and pharmaceutically-acceptable salts, hydrates and prodrug thereof,

in which

X is N or CH;

R<sub>1</sub> is hydrogen or C<sub>1-6</sub>alkyl or is taken together with R<sub>2</sub> or R<sub>3</sub> to form a monocyclic or bicyclic heteroaryl or heterocycle;

R<sub>2</sub> is hydrogen, aryl, cycloalkyl, heteroaryl, heterocyclo, or C<sub>1-6</sub>alkyl or C<sub>2-6</sub>alkenyl optionally substituted with one to three of hydroxy, halogen, aryl, cycloalkyl,

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heteroaryl, and/or heterocyclo; or  $R_2$  is joined together with  $R_1$  or  $R_3$  to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

$R_3$  is hydrogen or  $C_{1-6}$ alkyl or is taken together with  $R_2$  to form a monocyclic or bicyclic aryl, cycloalkyl, heteroaryl or heterocycle;

5  $R_8$  and  $R_9$  are independently selected from hydrogen, halogen, cyano, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclo, aryl, and heteroaryl;

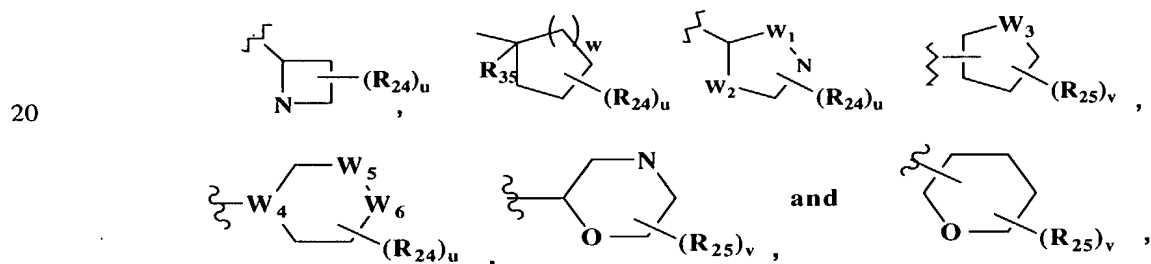
$R_{11}$  and  $R_{12}$  are selected independently of each other from hydrogen, alkyl, halogen, hydroxy, hydroxyalkyl, haloalkyl, amino, aminoalkyl, alkylamino, arylalkyl, cycloalkylalkyl, heteroarylalkyl, aryl, and cycloalkyl, or  $R_{11}$  and  $R_{12}$ , when  
10 attached to the same carbon atom, may join to form a spirocycloalkyl ring;

W is selected from:

1)  $-NR_{16}R_{17}$ ,  $-NR_{16}C(=O)R_{22}$ , or  $-NR_{16}CO_2R_{22}$ ; or

2) heteroaryl or heterocyclo groups selected from pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, isoxazolyl, thiazolyl, isothiazolyl, 3-azaisothiazolyl, pyridyl, pyrazinyl, pyridazinyl, 1,2-dihydropyridazinyl, and pyranal, wherein  
15 said heteroaryl and heterocyclo groups may be optionally substituted with one to three  $R_{36}$ , and may have an optionally-substituted carbocyclic, heterocyclic or heteroaryl ring fused thereto; or

3) a carbocyclic, heterocyclic, or heteroaryl ring selected from:



in which  $W_1$  and  $W_2$  are NH,  $CH_2$ , O or S,  $W_3$  is O or S,  $W_4$  is N or CH, and  $W_5$  and  $W_6$  are NH or  $CH_2$ , wherein when  $W_1$ ,  $W_2$ ,  $W_5$  and  $W_6$  are NH or  $CH_2$ , said groups are optionally substituted with  $R_{24}$ ;

25  $R_{16}$  and  $R_{17}$  are hydrogen,  $C_{1-8}$ alkyl or  $(CH_2)_q-J$ ,

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wherein J is selected from aryl, heteroaryl, heterocyclo, and cycloalkyl, wherein the alkyl, alkylene, and/or J groups of R<sub>16</sub> and/or R<sub>17</sub> are optionally substituted with up to three R<sub>32</sub>;

5 R<sub>22</sub> is selected from C<sub>1-6</sub>alkyl, trifluoromethyl, alkoxyalkyl, furylalkyl, alkylaminoethyl, phenyl, pyrrolylalkyl, piperidiny, and piperidinylalkyl, wherein R<sub>22</sub> in turn is optionally substituted with one to two C<sub>1-4</sub>alkyl and/or -CO<sub>2</sub>(C<sub>1-4</sub>alkyl);

R<sub>24</sub> and R<sub>25</sub> at each occurrence are attached to any available carbon or nitrogen atom of W and at each occurrence are selected from hydrogen, C<sub>1-6</sub>alkyl, halogen, substituted C<sub>1-6</sub>alkyl, amino, alkylamino, hydroxy, C<sub>1-4</sub>alkoxy, -C(=O)R<sub>26</sub>, -CO<sub>2</sub>R<sub>26</sub>,  
10 -SO<sub>2</sub>R<sub>26</sub>, -OR<sub>26</sub>, aryl, heteroaryl, heterocyclo, and cycloalkyl, and/or two R<sub>25</sub> attached to two adjacent carbon atoms or adjacent carbon and nitrogen atoms may join to form a fused optionally-substituted heteroaryl, heterocyclo or cycloalkyl ring, and/or two R<sub>24</sub> or two R<sub>25</sub> when attached to the same carbon atom may form keto (=O);

15 R<sub>26</sub> is alkyl, phenyl, benzyl, or aminoalkyl;

R<sub>32</sub> is selected from C<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkoxy, halogen, nitro, phenyl, benzyl, phenyloxy, benzyloxy, -C(=O)phenyl, amino, alkylamino, and aminoalkyl, wherein when R<sub>32</sub> includes a phenyl group said phenyl group in turn is optionally substituted with one to two of halogen, nitro, cyano, C<sub>1-4</sub> alkyl, and/or C<sub>1-4</sub>  
20 alkoxy;

R<sub>35</sub> and R<sub>36</sub> at each occurrence are selected from C<sub>1-6</sub>alkyl, halogen, substituted C<sub>1-6</sub>alkyl, hydroxy, alkoxy, cyano, trifluoromethyl, trifluoromethoxy, nitro, acyl, carboxyalkyl, sulfonyl, aryl, heteroaryl, heterocyclo, and cycloalkyl;

q is selected from 0, 1, 2 and 3;

25 r is 0 or 1;

s is 0 or 1;

u and v are 0, 1, or 2;

w is 0, 1, or 2; and

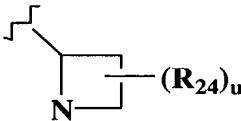
x is 0, 1, 2, 3, or 4.

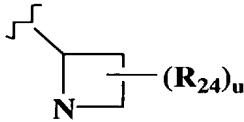


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- $R_{16}$  and  $R_{17}$  are independently selected from hydrogen,  $C_{1-8}$ alkyl, and  $(CH_2)_q$ -J, wherein J is selected from naphthyl, furanyl, indolyl, imidazolyl, pyrimidinyl, benzothiophenyl, pyridinyl, pyrrolyl, pyrrolidinyl, thiophenyl, and  $C_{3-7}$ cycloalkyl, wherein the alkyl, alkylene, and/or J groups of  $R_{16}$  and/or  $R_{17}$  are optionally substituted;
- $R_{22}$  is selected from  $C_{1-6}$ alkyl, trifluoromethyl, alkoxyalkyl, furylalkyl, alkylaminoethyl, phenyl, pyrrolylalkyl, piperidinyl, and piperidinylalkyl, wherein  $R_{22}$  in turn is optionally substituted with one to two  $C_{1-4}$ alkyl and/or  $-CO_2(C_{1-4}alkyl)$ ;
- $R_{24}$  is selected from keto ( $=O$ ),  $C_{1-6}$ alkyl, halogen, amino, aminoalkyl, alkylamino, hydroxy,  $C_{1-4}$ alkoxy, hydroxy $C_{1-4}$ alkyl,  $-C(=O)alkyl$ ,  $-C(=O)aminoalkyl$ ,  $-C(=O)phenyl$ ,  $-C(=O)benzyl$ ,  $-CO_2alkyl$ ,  $-CO_2phenyl$ ,  $-CO_2benzyl$ ,  $-SO_2alkyl$ ,  $-SO_2aminoalkyl$ ,  $-SO_2phenyl$ ,  $-SO_2benzyl$ , phenyl, benzyl, phenyloxy, benzyloxy, pyrrolyl, pyrazolyl, piperidinyl, pyridinyl, pyrimidinyl, and tetrazolyl, and each  $R_{24}$  in turn is optionally substituted with one to two  $R_{31}$ ;
- $R_{25}$  at each occurrence is attached to any available carbon or nitrogen atom of W and is selected from  $C_{1-6}$ alkyl, halogen, amino, aminoalkyl, alkylamino, hydroxy,  $C_{1-4}$ alkoxy, hydroxy $C_{1-4}$ alkyl,  $-C(=O)alkyl$ ,  $-C(=O)aminoalkyl$ ,  $-C(=O)phenyl$ ,  $-C(=O)benzyl$ ,  $-CO_2alkyl$ ,  $-CO_2phenyl$ ,  $-CO_2benzyl$ ,  $-SO_2alkyl$ ,  $-SO_2aminoalkyl$ ,  $-SO_2phenyl$ ,  $-SO_2benzyl$ , phenyl, benzyl, phenyloxy, benzyloxy, pyrrolyl, pyrazolyl, piperidinyl, pyridinyl, pyrimidinyl, and tetrazolyl, and/or two  $R_{25}$  when attached to adjacent carbon and/or nitrogen atoms may be taken together to form a fused benzo or pyrazolyl ring, and each  $R_{25}$  in turn is optionally substituted with up to two  $R_{31}$ ;
- $R_{30}$  is selected from  $C_{1-4}$ alkyl, hydroxy, alkoxy, halogen, nitro, cyano, amino, alkylamino, phenyl, and  $-C(=O)phenyl$ ;
- $R_{31}$  is selected from halogen, trifluoromethyl,  $C_{1-4}$ alkyl, hydroxy, and  $C_{1-4}$ alkoxy;
- w is selected from 0, 1, or 2;
- u and v are selected from 0, 1, and 2; and
- t is 0, 1 or 2.

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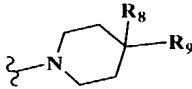
In compounds of formula (I), preferably W is ,  $-\text{NR}_{16}\text{R}_{17}$ , or  $\text{NR}_{16}\text{C}(=\text{O})\text{R}_{22}$ , wherein  $\text{R}_{16}$ ,  $\text{R}_{17}$ , and  $\text{R}_{22}$  are hydrogen, lower alkyl, phenyl, or lower alkyl substituted with phenyl, heterocyclo, or heteroaryl. More preferably W is  $\text{NH}_2$ ,

$\text{NH}(\text{lower alkyl})$ , or  $\text{N}(\text{lower alkyl})_2$ , or W is  wherein  $\text{R}_{24}$  is hydrogen or lower alkyl.

In compounds of formula (I), preferably  $\text{R}_{12}$  is hydrogen or lower alkyl, and  $\text{R}_{11}$  is preferably hydrogen, alkyl, heterocycloalkyl, heteroarylalkyl, or cycloalkylalkyl, more preferably imidazolylalkyl.

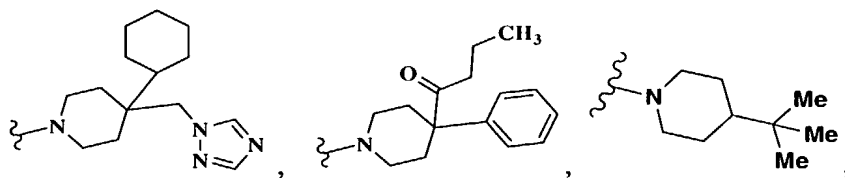
In compounds of formula (I), preferably  $\text{R}_2$  is arylalkyl, arylalkenyl, or heteroarylalkyl, more preferably thiazolyl or benzyl optionally substituted in the para position with lower alkyl, halogen, hydroxy, methoxy, cyano, trifluoromethyl, trifluoromethoxy, or nitro, more preferably chloro or fluoro.

In compounds of formula (I), preferably X is N,  $\text{R}_1$  is hydrogen or lower alkyl, and r and s are preferably 0.

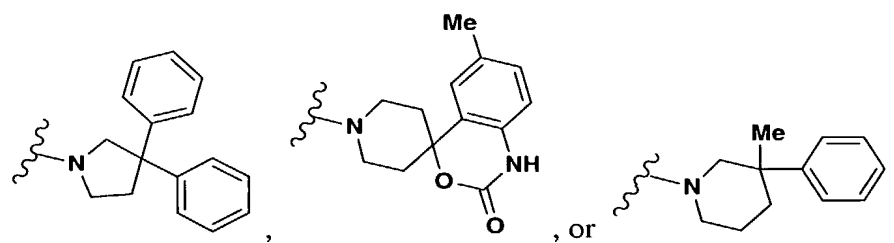
In compounds of formula (I), preferably E is , wherein  $\text{R}_8$  and  $\text{R}_9$  are selected independently from hydrogen, alkyl,  $-(\text{CH}_2)_j-\text{C}(=\text{O})\text{alkyl}$ ,  $-(\text{CH}_2)_j\text{-phenyl}$ ,  $-(\text{CH}_2)_j\text{-naphthyl}$ ,  $-(\text{CH}_2)_j\text{-C}_{4-7}\text{cycloalkyl}$ ,  $-(\text{CH}_2)_j\text{-heterocyclo}$ , and  $-(\text{CH}_2)_j\text{-}$

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heteroaryl, or  $R_8$  and  $R_9$  together form a spirocycloalkyl or spiroheterocyclic ring; and  $j$  is selected from 0, 1, 2 and 3. More preferably, E is

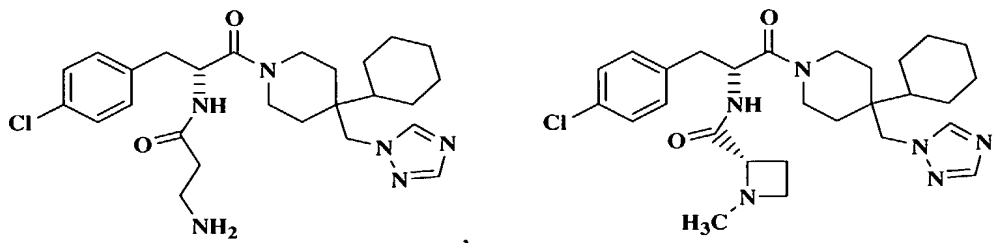


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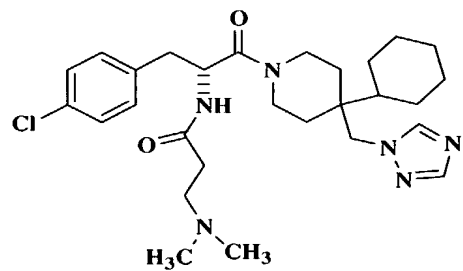
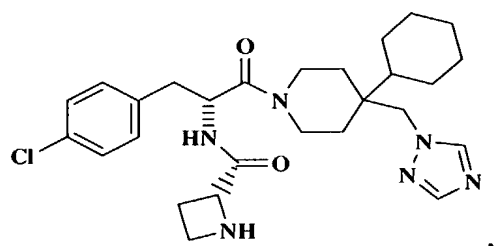
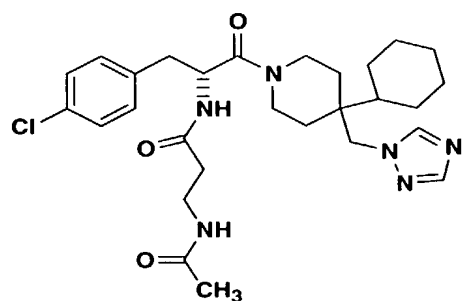
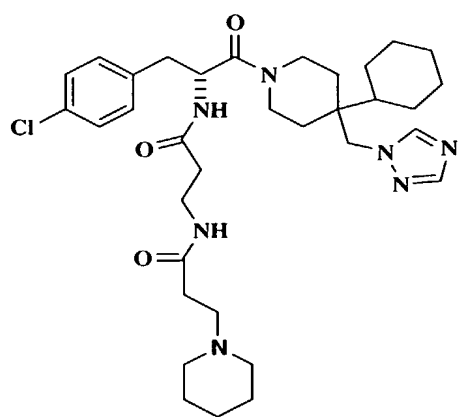
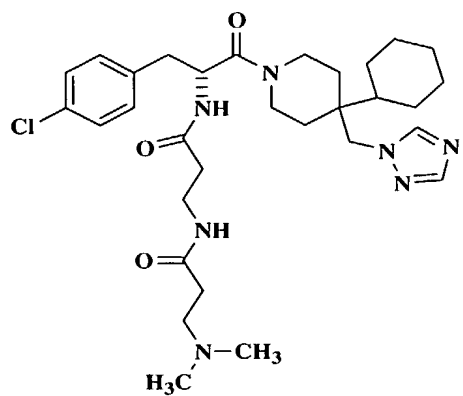
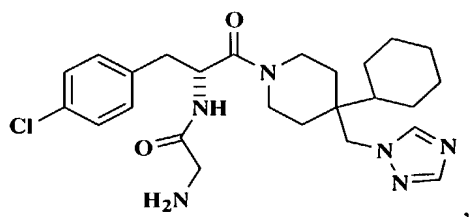


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Also preferred are compounds having the formulae:

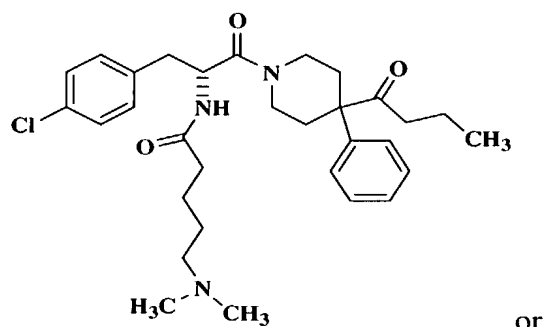
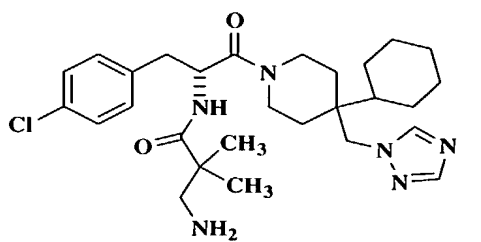
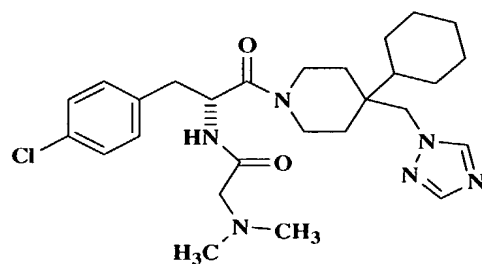
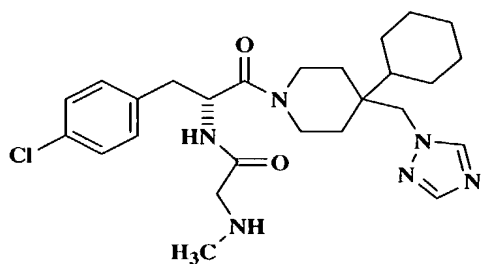
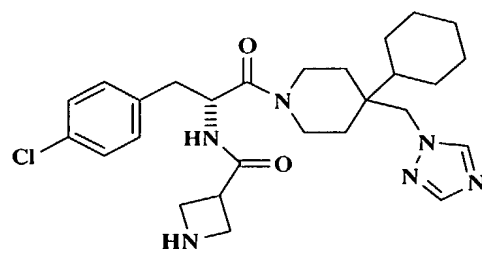
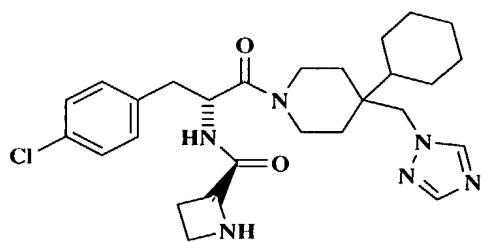


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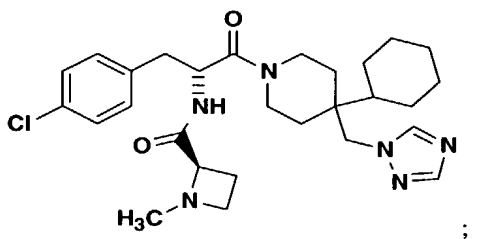




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or



and pharmaceutically-acceptable salts, hydrates and prodrugs thereof.

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### Utility

The inventive compounds are modulators of the melanocortin receptors MC-1R, MC-3R, MC-4R, and/or MC-5R. The compounds are useful in treating a wide range of

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condiitons responsive to regulation of the melanocortin receptors, including inflammatory and immune diseases, cardiovascular diseases, skin conditions, neurodegenerative conditions, sexual dysfunction, bodyweight disorders, and cancer. Certain compounds according to the invention have selective affinity for one melanocortin receptor relative to  
 5 the other melanocortin receptors and thus are particularly useful for treating those diseases responsive to regulation of that receptor. For example, certain compounds have high selectivity for binding to MC-1R relative to MC-3R, MC-4R, and MC-5R, and those compounds are particularly useful in treating inflammatory or immune conditions. Certain other compounds according to the invention have high selective affinity for MC-  
 10 4R and are particularly useful in treating bodyweight and/or neurodegenerative disorders. As used herein, the term “treating” or “treatment” refers to prophylaxis measures designed to inhibit or delay the onset of the disease or disorder and to responsive measures to alleviate, ameliorate, lessen, or cure the disease or disorder and/or its symptoms.

15 Compounds of the invention may be used to treat inflammation, particularly inflammation characterized by the activation of NF- $\kappa$ B and/or release of inflammatory cytokines. The compounds can be immunomodulators and have multiple effects on cells of the immune system. The compounds may be used to increase the levels of cAMP in cells (with resultant anti-inflammatory effects), decrease levels of the pro-inflammatory  
 20 messenger nitric oxide, decrease chemotactic ability, and alter the expression of immune-related genes for such agents as cytokines, adhesion molecules, and nitric oxide synthase.

In view of their effects on inhibiting NF- $\kappa$ B activity and suppressing cytokine accumulation, the compounds will be useful in treating consequences of many diseases associated with chronic and acute inflammation and immune-modulation. Such diseases  
 25 include, but are not limited to, inflammatory bowel disease, irritable bowel syndrome, gall bladder disease, Chrohn’s disease, rheumatoid arthritis, osteoarthritis, osteoporosis, traumatic arthritis, rubella arthritis, muscle degeneration, pancreatis (acute or chronic), psoriasis, glomerulonephritis, serum sickness, lupus (systematic lupus erythematosus), urticaria, scleraclerma, schleroderma, chronic thyroiditis, Grave’s disease, dermatitis

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(contact or atopic), dermatomyositis, alopecia, atopic eczemas, ichthyosis, fever, sepsis, migraine, cluster headaches, Alzheimer's Disease, Parkinson's disease, Creutzfeldt-Jacob disease, multiple sclerosis, tuberculosis, dementia, and transplant or graft-host rejections (*e.g.*, kidney, liver, heart, lung, pancreas, bone marrow, cornea, small bowel, skin

5 allografts, skin homografts and heterografts, etc.). The compounds may also be used to treat respiratory allergies and diseases including asthma, acute respiratory distress syndrome, hayfever, allergic rhinitis, and chronic obstructive pulmonary disease; and inflammatory disorders of the central nervous system, including HIV encephalitis, cerebral malaria, meningitis, and ataxia telangiectasis. Additionally, the compounds may

10 be useful in treating pain, *e.g.*, post-operative pain, neuromuscular pain, headache, pain caused by cancer, dental pain, and arthritis pain.

In view of their activity in inhibiting NF- $\kappa$ B activity, the compounds may be used to treat viral and autoimmune diseases including herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), cytomegalovirus, Epstein-Barr, human immunodeficiency virus

15 (HIV), Addison's disease (autoimmune disease of the adrenal glands), idiopathic adrenal insufficiency, autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), chronic active hepatitis or acute hepatitis infection (including hepatitis A, hepatitis B, and hepatitis C), autoimmune gastritis, autoimmune hemolytic anemia, and autoimmune neutropenia. The compounds of the invention may also be used

20 to treat fungal infections such as mycosis fungoides.

In addition, the compounds of this invention are useful in treating diseases of the cardiovascular system including those diseases in which inflammation is an underlying component. These diseases include but are not limited to atherosclerosis, transplant atherosclerosis, peripheral vascular disease, inflammatory vascular disease,

25 intermittent claudication, restenosis, cerebrovascular stroke, transient ischemic attack, myocardial ischemia and myocardial infarction. The compounds also may be used to treat hypertension, hyperlipidemia, coronary artery disease, unstable angina, thrombosis, thrombin-induced platelet aggregation, and/or consequences occurring from thrombosis and/or the formation of atherosclerotic plaques.

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Additionally, the compounds may be useful to treat stroke and other ischemic brain diseases and/or neurodegeneration associated therewith, and the neurodegeneration of, or consequences of, traumatic brain injury.

In view of their ability to act as immunomodulators in the skin and affect the  
5 production of melanin in the skin, the compounds are useful in altering pigmentation in the skin and may be used as photoprotective agents including agents for preventing, treating, or ameliorating sunburn. The compounds also may be used in treating acne, vitiligo, alopecia areata, photosensitivity disorders, albinism, and porphyria. Additionally, the compounds are useful to promote cosmetic as well as therapeutic  
10 tanning.

The compounds of the invention may also be used to treat neurodegenerative disorders including depression, anxiety, compulsion (obsessive-compulsive disorder), neuroses, psychosis, insomnia/sleep disorder, sleep apnea, and drug or substance abuse.

The compounds of the invention may be used to treat male or female sexual  
15 dysfunction. Male sexual dysfunction includes impotence, loss of libido, and erectile dysfunction (including but not limited to ejaculatory failure, premature ejaculation, or an inability to achieve or maintain an erection or inability to achieve an orgasm). Female sexual dysfunction may include sexual arousal disorder or disorders relating to desire, sexual receptivity, orgasm, and/or disturbances in trigger points of sexual function.  
20 Female sexual dysfunction may also include sexual pain, premature labor, dysmenorrhea, excessive menstruation, and endometriosis.

The compounds of the invention may also be used to treat bodyweight disorders including but not limited to obesity and anorexia (*e.g.*, by altering appetite, metabolic rate, fat intake or carbohydrate craving); and diabetes mellitus (by enhancing glucose  
25 tolerance and/or decreasing insulin resistance).

The compounds also may be used to treat cancer, more particularly, cancer of the lung, prostate, colon, breast, ovaries, and bone, or angiogenic disorders including the formation or growth of solid tumors.

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The compounds of the invention may also be used to treat veterinary disease such as veterinary viral infections, including feline immunodeficiency virus, bovine immunodeficiency virus, and canine immunodeficiency virus.

5 The term “melanocortin-receptor associated condition” when used herein refers to each of the above-referenced conditions, disorders, or diseases that may be treated by agonizing or antagonizing a melanocortin receptor, inhibiting NF- $\kappa$ B activity and/or suppressing cytokine accumulation as if each of these conditions, disorders and diseases were set forth herein at length.

10 The inventive compounds may be used alone or in combination with each other and/or other therapeutic agents such as anti-inflammatory drugs, antibiotics, anti-viral agents, anti-fungal agents, anti-diabetic agents, anti-osteoporosis agents, anti-obesity agents or appetite suppressants, growth promoting agents (including growth hormone secretagogues), anti-anxiety agents, anti-depressants, anti-hypertensive agents, cholesterol/lipid lowering agents, bone resorption inhibitors, and anti-tumor agents  
15 including antiproliferative agents, or cytotoxic drugs.

Examples of suitable other anti-inflammatory agents with which the inventive compounds may be used include aspirin, non-steroidal antiinflammatory drugs (NSAIDs) (such as ibuprofen and naproxin), TNF- $\alpha$  inhibitors (such as tenidap and rapamycin or derivatives thereof), or TNF- $\alpha$  antagonists (*e.g.*, infliximab, OR1384), prednisone,  
20 dexamethasone, Enbrel®, cyclooxygenase inhibitors (*i.e.*, COX-1 and/or COX-2 inhibitors such as Naproxen®, Celebrex®, or Vioxx®), CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, IMPDH inhibitors, such as mycophenolate (CellCept®), integrin antagonists, alpha-4 beta-7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, prostaglandin synthesis inhibitors, budesonide,  
25 clofazimine, CNI-1493, CD4 antagonists (*e.g.*, priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, therapies for the treatment of irritable bowel syndrome (*e.g.*, Zelmac® and Maxi-K® openers such as those disclosed in U.S. Patent No. 6,184,231 B1), or other NF- $\kappa$ B inhibitors, such as

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corticosteroids, calphostin, CSAIDs, 4-substituted imidazo [1,2-A]quinoxalines as disclosed in US Pat. No. 4,200,750; Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; and nuclear translocation inhibitors, such as deoxyspergualin (DSG). To treat pain such as migraine and other headaches, the  
 5 inventive compounds may be used in combination with aspirin, NSAIDs, or with 5-HT<sub>1D</sub> receptor agonists such as sumatriptan, eletriptan or rizatriptan.

Examples of suitable other antibiotics with which the inventive compounds may be used include  $\beta$ -lactams (*e.g.*, penicillins, cephalosporins and carbopenams);  $\beta$ -lactam and lactamase inhibitors (*e.g.*, augamentin); aminoglycosides (*e.g.*, tobramycin and  
 10 streptomycin); macrolides (*e.g.*, erythromycin and azithromycin); quinolones (*e.g.*, cipro and tequin); peptides and depeptides (*e.g.* vancomycin, synergid and daptomycin) metabolite-based anti-biotics (*e.g.*, sulfonamides and trimethoprim); polyring systems (*e.g.*, tetracyclins and rifampins); protein synthesis inhibitors (*e.g.*, zyvox, chlorphenicol, clindamycin, etc.); and nitro-class antibiotics (*e.g.*, nitrofurans and nitroimidazoles).

15 Examples of suitable other antifungal agents with which the inventive compounds may be used include fungal cell wall inhibitors (*e.g.*, candidas), azoles (*e.g.*, fluconazole and vericonazole), and membrane disruptors (*e.g.*, amphotericin B).

Examples of suitable other antiviral agents for use with the inventive compounds include nucleoside-based inhibitors, protease-based inhibitors, and viral-assembly  
 20 inhibitors.

Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include biguanides (*e.g.*, metformin or phenformin), glucosidase inhibitors (*e.g.*, acarbose or miglitol), insulins (including insulin secretagogues, sensitizers or mimetics), meglitinides (*e.g.*, repaglinide), sulfonylureas  
 25 (*e.g.*, glimepiride, glyburide, gliclazide, chlorpropamide and glipizide), biguanide/glyburide combinations (*e.g.*, Glucovance®), thiazolidinediones (*e.g.*, troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, glycogen phosphorylase



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Examples of suitable anti-anxiety agents for use in combination with the compounds of the present invention include benzodiazepines, diazepam, lorazepam, buspirone (Serzone®), oxazepam, and hydroxyzine pamoate, or dopamine receptor agonists.

5           Examples of suitable anti-depressants for use in combination with the compounds of the present invention include citalopram, fluoxetine, nefazodone, sertraline, and paroxetine.

In treating skin disorders or diseases as described above, the compounds may be used alone or in combination with a retinoid, such as tretinoin, or a vitamin D analog.

10           Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid, tricyclic, chlorthalidone, furosemide, 15 musolimine, bumetanide, triamterene, amiloride, and spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, Vanlev®, pravastatin, zofenopril, fosinopril, enalapril, ceranopril, cilazapril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrisentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 20 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopeptidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), nitrates, and cardiac glycosides (e.g., digitalis and ouabain).

25           Examples of suitable cholesterol/lipid lowering agents for use in combination with the compounds of the present invention include HMG-CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, an ileal Na<sup>+</sup>/bile acid cotransporter inhibitor,



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cholesterol absorption inhibitors, and cholesterol ester transfer protein inhibitors (*e.g.*, CP-529414).

In addition, the compounds may be used with other agents to increase the levels of cAMP or cGMP in cells for a therapeutic benefit. For example, applicants have  
5 discovered that MC-1R agonists including the compounds of the invention have advantageous effects when used in combination with phosphodiesterase inhibitors, including PDE1 inhibitors (such as those described in Journal of Medicinal Chemistry, Vol. 40, pp. 2196-2210 [1997]), PDE2 inhibitors, PDE3 inhibitors (such as revizinone, pimobendan, or olprinone), PDE4 inhibitors (such as rolipram, cilomilast, or piclamilast),  
10 and PDE7 inhibitors. The compounds of this invention also may be used in combination with PDE5 inhibitors such as sildenafil, sildenafil citrate, (*e.g.*, when treating sexual dysfunction) or IC-351.

The combination of the inventive compounds with other therapeutic agents may prove to have additive and synergistic effects. The combination may be advantageous to  
15 increase the efficacy of the administration or decrease the dosage to reduce possible side-effects.

The compounds of formula I may be administered by any means suitable for the condition to be treated. The compounds may be delivered orally such as in the form of tablets, capsules, granules, powders, or with liquid formulations including syrups;  
20 sublingually; buccally; transdermally; parenterally such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion (*e.g.*, as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; rectally such as in the form of suppositories; or liposomally. Dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents may be administered. The  
25 compounds may be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved with suitable pharmaceutical compositions or, particularly in the case of extended release, with devices such as subcutaneous implants or osmotic pumps.

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Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may

5 contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The inventive compounds may be orally delivered by sublingual and/or buccal administration, *e.g.*, with molded, compressed, or freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such

10 as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (*e.g.*, GANTREZ®); and agents to control

15 release such as polyacrylic copolymer (*e.g.*, CARBOPOL 934®). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other

20 solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending

25 agents, including synthetic mono- or diglycerides and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, synthetic

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glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art. The specific dose level and frequency of dosage for any particular subject may vary and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. An exemplary effective amount of compounds of formula I may be within the dosage range of about 0.1 to about 100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg (or from about 1 to about 2500 mg, preferably from about 5 to about 2000 mg) on a regimen in single or 2 to 4 divided daily doses. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats, horses, and the like, subject to melanocortin-receptor associated conditions.

Each of the inventive compounds exemplified herein has been tested and shown activity at a measurable level for modulating a melanocortin receptor, according to an assay described below and/or an assay known in the field, such as, for example, assays described in WO 00/74679 A1 and WO 01/91752.

## 20 Assays

### MC1R

HBL cells, a human melanoma cell line licensed from Prof. G. Ghanem (Lab. of Oncology & Exp. Surgery, Free University of Brussels, Brussels, Belgium) were used as a source of the human MC-1R. cAMP was measured using the cAMP SPA Direct Screening Assay System from Amersham (RPA 559). 20,000 HBL cells were plated into each well of a half-area 96 well white plate and were used between 16-48 hours after plating. Cells were incubated at 37°C for 15 minutes in 25 uM IBMX to inhibit phosphodiesterase activity. As per kit instructions, Assay Buffer Concentrate was diluted

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1 to 50 with dH<sub>2</sub>O to prepare Assay Buffer (50 mM acetate buffer containing 0.01% sodium azide). Vials containing rabbit anti-succinyl cAMP serum and the tracer, adenosine 3',5'-cyclic phosphoric acid 2'-O-succinyl-3-[<sup>125</sup>I] iodotyrosine methyl ester, were resuspended with 7.5 ml Assay Buffer. SPA anti-rabbit reagent (donkey anti-rabbit IgG coupled to SPA PVT beads) was resuspended with 15 ml Assay Buffer. All reagents were stored at 4°C after reconstitution. Melanocortin ligands or compounds were prepared in DMSO and added to the IBMX-treated cells as 100X concentrated stocks. 50 nM α-MSH was used for the maximum response and 1 ul DMSO was included in the negative control wells. The final concentration of DMSO was 1% in all the samples.

After 15-30 minutes of stimulation, the reaction was terminated by the aspiration of the contents of the well followed by addition of 15 ul Assay Buffer containing 0.1 N HCl. Plates were kept at room temperature for at least 30 minutes to effect extraction of cAMP. Antiserum, Tracer, and SPA anti-rabbit reagent solutions were mixed 1:1:1 just prior to use. 15 ul of SPA reagent mixture was dispensed into each well and plates were incubated at room temperature for a minimum of 5 hours. Plates were subsequently counted for 6 minutes per sample in a TopCount scintillation reader with background subtraction. Data was analyzed in relation to a cAMP standard curve.

#### **MC-4R**

##### **A. Binding Assay.**

The membrane binding assay may be used to identify competitive inhibitors of [<sup>125</sup>I]NDP-α-MSH binding to cloned human MC4R expressed in Hi5 insect cells infected by a baculovirus/human MC4R receptor construct.

Hi5 cells are grown in suspension in Express Five SFM Insect Cell Media (Gibco, Cat. No. 10486-025) at 27°C with constant shaking. Hi5 cells are infected using the following protocol:

- Cells at a density of  $1 \times 10^6$  cells/mL are spun down at 1000 rpm (Beckman GS-6KR centrifuge) for 10 minutes.

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- Cells are resuspended in 10% of their original volume in a sterile 50 mL conical centrifuge tube wrapped with aluminum foil. Virus is added at a Multiplicity of Infection (MOI) of 3 and incubated for 1 hour at room temperature with gentle shaking.

- This cell/virus mix is added to the appropriate volume of medium to attain the  
5 original volume and incubated at 27°C with constant shaking for 72 hours.

- Cells are spun down in 50 mL conical centrifuge tubes at 1000 rpm for 10 minutes. Each of the resulting pellets are resuspended in 10 mL of cold (4°C) membrane buffer (25 mM HEPES, pH 7.4, 140 mM NaCl, 1.2 mM MgCl<sub>2</sub>, 2.5 mM CaCl<sub>2</sub>, 10 µG/mL Aprotinin, 10 µG/mL Leupeptin) and Dounce homogenized using 10-12 strokes.  
10 Dilute to 30 mL with buffer and centrifuge at 18,000 rpm, 4°C, 15 minutes (Sorvall RC5C Centrifuge). The resulting pellet is resuspended in cold membrane buffer in a total of ¼ of the original volume by vortexing and aspiration using a syringe and 27 gauge needle.

Protein content is determined (Bradford, Bio-Rad Protein Assay). Membranes are  
15 aliquoted in microcentrifuge tubes and quick frozen in liquid nitrogen. Store at -80°C until use.

The membrane binding buffer is composed of 25 mM HEPES, pH 7.4, 140 mM NaCl, 1.2 mM MgCl<sub>2</sub>, 2.5 mM CaCl<sub>2</sub>, 0.1% BSA. 160 µL of membrane binding buffer containing 0.5 µg membrane protein is added to 20 µL of 1.0 nM [<sup>125</sup>I]-NDP-α-MSH  
20 (final concentration is 0.1 nM) and 20 µL of competing drug or buffer and incubated for 90 minutes at 37 °C.

The mixture is filtered with Brandel Microplate 96 filter apparatus using 96-well GF/B filter presoaked in 1-% polyethyleneimine (Sigma). The filter is washed (4 times with a total of 1 mL per well) with cold wash buffer consisting of 20 mM HEPES, pH  
25 7.4, 5 mM MgCl<sub>2</sub>.

The filter is dried and punched into a 96 well sample plate (Wallac, 1450-401). 100 µl of Wallac Optiphase Supermix scintillation fluid is added to each well. The top is

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sealed and the plates are shaken to insure that the filters are thoroughly soaked with fluid. Plates are then counted in a Wallac Microbeta Trilux Scintillation and Luminescence Counter (Model 1450). Dose-response curves are fitted by linear regression analyses and IC<sub>50</sub> values are calculated using ExcelFit.

5           B.           Functional assay.

Functional membrane based [<sup>35</sup>S]GTPγS binding assays are developed to discriminate agonists and antagonists.

Membrane preparation. Cells (HEK-293 cells expressing the human MC4R) are grown in Minimum Essential Medium with Earle's salts and L-glutamate (Life Technologies, Cat. # 11095-080) containing 10% heat-inactivated fetal bovine serum, 400 μg/mL geneticin and 100 mM sodium pyruvate in T175 flasks. Upon reaching confluence, cells are dissociated from tissue culture flasks by rinsing with Ca<sup>2+</sup> and Mg<sup>2+</sup> free phosphate buffered saline (Life Technologies, Cat. # 14190-144) and detached following 5 minutes incubation at 37°C with enzyme free cell dissociation buffer (Life Technologies, Cat. # 13151-014). Cells are collected by centrifugation and resuspended in membrane preparation buffer consisting of 20 mM HEPES, pH 7.4, 10 mM EDTA, 10 μg/mL aprotinin and 10 μg/mL leupeptin. The suspension is homogenized by polytron PT3000 for 30 sec at 20,000 rpm, and centrifuged at 35,000 x g for 15 minutes at 4 °C. The pellet is resuspended in membrane preparation buffer and the last centrifugation is repeated. The final pellet is resuspended in membrane storage buffer consisting of 20 mM HEPES, pH 7.4, 0.1 mM EDTA, 10 μg/mL aprotinin and 10 μg/mL leupeptin. Protein concentration is determined by the Bio-Rad method (Bio-Rad, Cat.# 500-0006) and the preparation is diluted to a final protein concentration of 1 mg/mL. Aliquots are stored at -70°C until used.

25           [<sup>35</sup>S]GTPγS membrane binding assay. Compounds are dissolved at 10 mM concentration in DMSO and diluted to the required concentration into assay buffer. GTPγS to determine nonspecific binding is prepared at 100 μM concentration in assay buffer. The final concentration of DMSO in the assay is 1%. The assay buffer is

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consisting of 20 mM HEPES, pH 7.4, 100 mM NaCl, 5 mM MgCl<sub>2</sub>, 0.5 μM GDP, 10 μg/mL saponin, 10 μg/mL aprotinin and 10 μg/mL leupeptin. The assay is composed by adding 50 μL 10X drug solution, 200 μL membrane preparation (containing 2-4 μg protein), 50 μL [<sup>35</sup>S]GTPγS (100,000-150,000 CPM) and 200 μL assay buffer to achieve  
 5 a total volume of 500 μL. The assay mixture is incubated at room temperature for exactly 30 minutes. The reaction is terminated by rapid filtration under vacuum through Whatman GF/B filters using a Brandel 96 wells cell harvester, followed by washing four times with cold wash buffer consisting of 20 mM HEPES, pH 7.4, and 5 mM MgCl<sub>2</sub>. The filters are air-dried and 200μL Wallac, Optiphase Super Mix, liquid scintillation cocktail  
 10 is added to each filter. The bound radioactivity (CPM) is determined by Wallac Trilux 1450 MicroBeta liquid scintillation and Luminescence counter after six hours.

Data interpretation. NDP-α-MSH is used as reference compound and its maximal stimulation is measured at 1 μM (Ref CPM 100%). Total drug-independent binding (Total CPM) is measured in the absence of compounds. Response triggered by  
 15 compounds is expressed as percent NDP-α-MSH response. Compound dose response curves are generated by Excel XL Fit. The top of the curve represents the compound's intrinsic activity expressed as % of maximal stimulation.

#### C. Radioligand binding assays.

Binding of [<sup>125</sup>I]-(Nle<sup>4</sup>, D-Phe<sup>7</sup>)-α-MSH to human melanocortin receptors was  
 20 performed using membrane homogenates from Hi5 cells that express recombinant MC4 receptors (Hi5-MC4 cells) and from HEK-293 cells that express recombinant MC3 receptors (HEK-MC3 cells) or MC5 receptors (HEK-MC5 cells) as well as from HBL cells expressing the human MC1R receptor. Homogenates (~0.5 μg protein/well) were incubated with [<sup>125</sup>I]-(Nle<sup>4</sup>,D-Phe<sup>7</sup>)-α-MSH (100 pM for assays with MC4 receptors and  
 25 50 pM for assays with MC3/5 receptors) and increasing concentrations of competitors (final concentration of DMSO = 1%) for 90 min at 37°C in buffer consisting of 25 mM HEPES (pH 7.4), 140 mM NaCl, 2.5 mM CaCl<sub>2</sub>, 1.2 mM MgCl<sub>2</sub> and 0.1% BSA (10 μg/ml aprotinin and 10 μg/ml leupeptin were added to assays with MC3/5 receptors).

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Assays were stopped by addition of cold wash buffer (20 mM HEPES and 5 mM MgCl<sub>2</sub> for assays with MC4 receptors and 20 mM HEPES for assays with MC3/5 receptors).

Filtration over glass fiber filters (Whatman GF/B previously soaked in 1% PEI for assays with MC4 receptors or 0.5% PEI for assays with MC3/5 receptors) was performed using a

5 Brandel cell harvester. Non-specific binding was defined with 1  $\mu$ M NDP- $\alpha$ -MSH.

### **Abbreviations**

Boc = tert-butoxycarbonyl  
 CBZ =benzyloxycarbonyl  
 10 DCE = 1,2-dichloroethane  
 DCM = dichloromethane  
 DEA = diethylamine  
 DMAP = 4-dimethylaminopyridine  
 DMF = N,N-dimethylformamide  
 15 DMSO = dimethylsulfoxide  
 EDC or EDCI = 3-ethyl-3'-(dimethylamino)propyl-carbodiimide hydrochloride  
 Et = ethyl  
 EtOH = ethanol  
 EtOAc = ethyl acetate  
 20 Et<sub>3</sub>N = triethylamine  
 EtOAc = ethyl acetate  
 Et<sub>2</sub>O = diethyl ether  
 Fmoc = fluorenylmethoxycarbonyl  
 HCl = hydrogen chloride  
 25 HOBt or HOBT = hydroxybenzotriazole hydrate  
 LiOH = lithium hydroxide  
 Na<sub>2</sub>SO<sub>4</sub> = sodium sulfate  
 NaOH = sodium hydroxide  
 NMM = N-methylmorpholine  
 30 Me = methyl  
 MeOH = methanol  
 Ph = phenyl  
 THF = tetrahydrofuran  
 TFA = trifluoroacetic acid  
 35 mp = melting point  
 tlc = thin layer chromatography  
 RT = room temperature  
 h = hours  
 min. = minute or minutes  
 40 mmol = millimole



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sat'd = saturated

 $\text{CH}_2\text{Cl}_2$  = methylene chloride

HPLC = high pressure liquid chromatography

LRMS = low resolution mass spectrometry

5

In the examples, when a letter is used in a parenthetical or superscript following the term HPLC, MS, or HPLC/MS, as in "HPLC/MS (A)", "LC/MS (B)", MS Data<sup>a</sup>, or following the data, such as 3.28<sup>a</sup>, the letter denotes the conditions used for the HPLC/MS, as follows:

10

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**Method A:** Column Primesphere C18-HC 4.6 x 30 mm, gradient time: 2 min., Hold time: 1 min., Flow rate: 4 mL / min, Detector Wavelength: 220 nM, Solvent A = 10 % AcCN / 90 % H<sub>2</sub>O / 5mM NH<sub>4</sub>OAc, Solvent B = 90 % AcCN / 10 % H<sub>2</sub>O / 5mM NH<sub>4</sub>OAc, Start % B = 0 / Finish % B = 100;

**Method B:** Column Primesphere C18-HC 4.6 x 30 mm, gradient time: 2 min., Hold time: 1 min., Flow rate: 4 mL / min, Detector Wavelength: 220 nM, Solvent A: 10 % AcCN / 90 % H<sub>2</sub>O / 0.1 % TFA, Solvent B: 90 % AcCN / 10 % H<sub>2</sub>O / 0.1 % TFA, Start % B = 0 / Finish % B = 100;

**Method C:** Column Primesphere C18-HC 4.6 x 30 mm, gradient time: 3 min., Hold time: 1 min., Flow rate: 4 mL / min, Detector Wavelength: 220 nM, Solvent A: 10 % AcCN / 90 % H<sub>2</sub>O / 0.1 % TFA, Solvent B: 90 % AcCN / 10 % H<sub>2</sub>O / 0.1 % TFA, Start % B = 0 / Finish % B = 100, Detector Wavelength: 220 nM;

**Method D:** Column: Premisphere 5 $\mu$ -C8 21 x 100 mm, acetonitrile-5 mM NH<sub>4</sub>OAc/water: 7 min. gradient from 20% AcCN to 90% AcCN at 220 nm. Flow rate: 20 mL/min.);

**Method E:** Column: YMC ODS-A C18 4.6 x 150 mm; Flow rate: 1 mL / min, Solvent system: 0-100% B in 30 min. Solvent A: 10% CH<sub>3</sub>CN - 90 % H<sub>2</sub>O – 5 mM NH<sub>4</sub>OAc; Solvent B: 90% CH<sub>3</sub>CN - 10 % H<sub>2</sub>O – 5mM NH<sub>4</sub>OAc; UV: 220 nm;

**Method F:** Column: Combiscreen C8 S-5 4.6 x 50 mm; Flow rate: 4 mL / min, Solvent system: 0-100% B in 2 min. Solvent A: 10% CH<sub>3</sub>CN - 90 %H<sub>2</sub>O – 5mM NH<sub>4</sub>OAc; Solvent B: 90% CH<sub>3</sub>CN - 10 %H<sub>2</sub>O – 5mM NH<sub>4</sub>OAc; UV: 220 nm;

**Method G:** Column: Combiscreen C8 S-5 4.6 x 50 mm; Flow rate: 4 mL / min, Solvent system: 0-100% B in 4 min. Solvent A: 10% CH<sub>3</sub>CN - 90 % H<sub>2</sub>O – 0.1% TFA; Solvent B: 90% CH<sub>3</sub>CN - 10 % H<sub>2</sub>O – 0.1% TFA; UV: 220 nm;

**Method H:** Column: YMC ODS-A C18 4.6 x 150 mm; Flow rate: 1 mL / min, Solvent system: 30-100% B in 30 min. Solvent A: 10% CH<sub>3</sub>CN - 90 %H<sub>2</sub>O – 0.1% TFA; Solvent B: 90% CH<sub>3</sub>CN - 10 % H<sub>2</sub>O – 0.1% TFA; UV: 220 nm;

**Method I:** Assignment from another HPLC analysis (with 0.1 % TFA);

**Method J:** Column: Premisphere-5u C8 4.6 x 30 mm; Flow rate: 4 mL / min, Solvent system: 0-100% (90% CH<sub>3</sub>CN - 10 %H<sub>2</sub>O – 5mM NH<sub>4</sub>OAc), 2 min. gradient; UV: 220 nm;

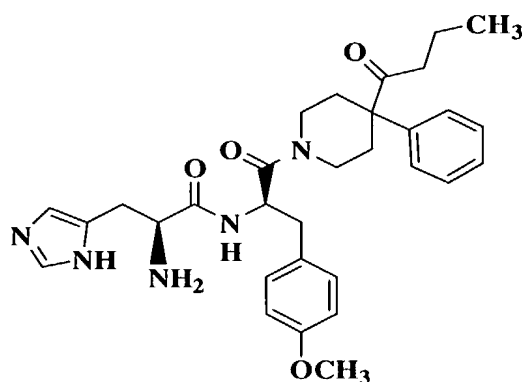
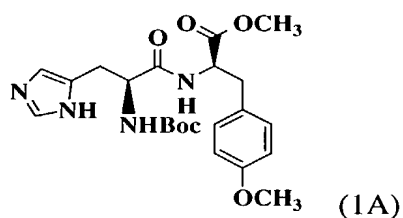
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**Method K:** Column: YMC S5 C18 4.6 x 150 mm; Flow rate: 1 mL / min, Solvent system: 0-100% B (90% CH<sub>3</sub>CN - 10 %H<sub>2</sub>O – 5mM NH<sub>4</sub>OAc), 30 min. gradient; UV: 220 nm;

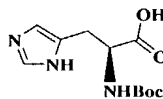
5 **Method L:** Column: Xterra- C8 4.6 x 30 mm; Flow rate: 4 mL / min, Solvent system: 0-100% B in 2 min. Solvent A: 10% CH<sub>3</sub>CN - 90 %H<sub>2</sub>O – 5mM NH<sub>4</sub>OAc; Solvent B: 90% CH<sub>3</sub>CN - 10 %- 5<sub>2</sub>O – 5mM NH<sub>4</sub>OAc; UV: 220 nm;

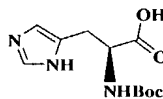
10 **Method M:** Column: YMC-Pack S5 Phenyl 4.6 x 50 mm; Flow rate: 3 mL / min, Solvent system 0-100% B in 2 min. Solvent A: 10% CH<sub>3</sub>CN - 90 % H<sub>2</sub>O – 0.05 % TFA; Solvent B: 90% CH<sub>3</sub>CN - 10 %H<sub>2</sub>O – 0.05 % TFA; UV: 220 nm.

15

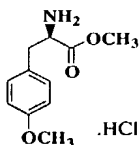
**EXAMPLE 1****Step A:**

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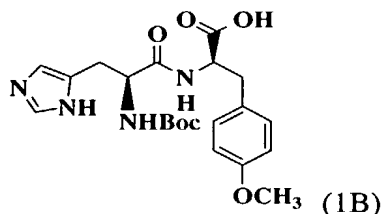
To a solution of N-Boc-L-histidine [  ] (3.1 g, 12.7 mmol), EDC (3.6 g, 19.1 mmol), HOBT (2.6 g, 19.1 mmol), DMAP (0.16 g, 1.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub>, and DMF (1:1, 50 mL) were added Et<sub>3</sub>N (8.8 mL, 64.0 mmol) and D-4-methoxyphenylalanine

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methylester hydrochloride [ COc1ccc(cc1)C[C@H]2CCNC(=O)OC2 .HCl ] (2.9 g, 12.0 mmol), sequentially. The reaction mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc (200 mL) and washed with water (200 mL), NaOH (0.5 N, 200 mL), and water (200 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was subsequently removed under reduced pressure. The resulting compound 1A was >90% pure as judged by HPLC and used without further purification in Step B.

### Step B:



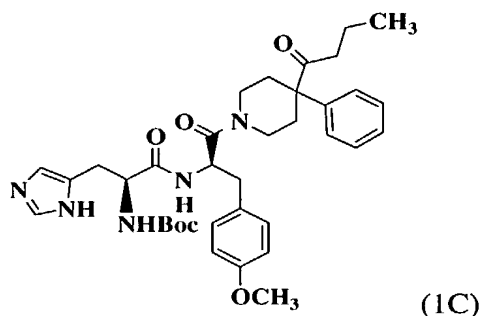
10

To a solution of Compound 1A (12.0 mmol) in CH<sub>3</sub>OH (13 mL) was added NaOH (2N, 13 mL) to make the final concentration of NaOH ~1 N. This solution was stirred at RT for 2 h before being diluted with water (100 mL). The aqueous layer was extracted with Et<sub>2</sub>O (100 mL X 2), and the organic matter was discarded. The aqueous layer was acidified with HCl (6 N) to pH ~ 2, and extracted with EtOAc (100 mL X 2). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was subsequently removed under reduced pressure. The resulting Compound 1B was a white solid with a purity >90% as judged by HPLC. This intermediate was used without further purification for Step C.

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### Step C:

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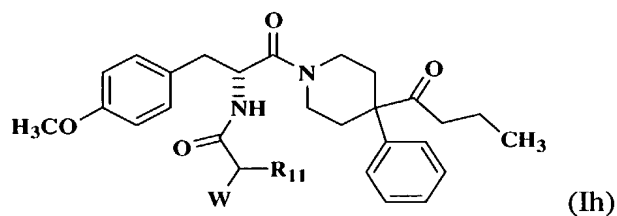
To a solution of Compound 1C (0.5 g, 1.1 mmol), EDC (0.3 g, 1.6 mmol),  
 5 HOBT (0.22 g, 1.6 mmol), and DMAP (0.13 g, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) were added  
 Et<sub>3</sub>N (0.8 mL, 5.5 mmol) and 4-butyryl-4-phenyl-piperidine hydrochloride (0.35 g, 1.3  
 mmol) sequentially. The reaction mixture was stirred at RT overnight. The reaction  
 mixture was diluted with EtOAc (100 mL) and washed with HCl (0.5 N, 100 mL), water  
 (100 mL), NaOH (0.5 N, 100 mL), and water (100 mL). The organic layer was dried over  
 10 anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was subsequently removed under reduced pressure.  
 The resulting Compound 1C was >90% pure as judged by HPLC and used directly  
 without further purification in Step D.

**Step D:** Deprotection of Compound 1C

15

To a solution of the Boc-protected Compound 1C (1.1 mmol) in wet CH<sub>2</sub>Cl<sub>2</sub> (20  
 mL plus 1 mL water) was added TFA (10 mL). The solution was stirred at RT for 1 h  
 before the solvents were removed. The crude reaction mixture was purified by  
 preparative HPLC to obtain Example 1 at >95% purity as judged by HPLC. HPLC (min)  
 20 = 2.5, MS (M+H)<sup>+</sup> = 546.4.

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**EXAMPLES 2-84**

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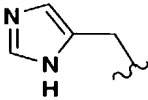

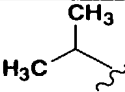

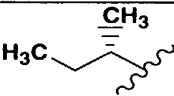

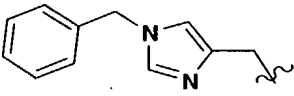

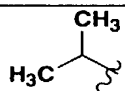
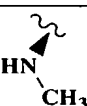
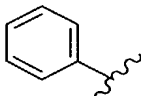

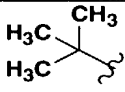

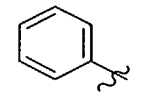

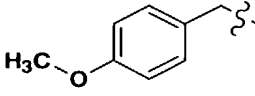

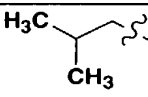

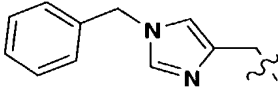

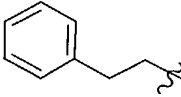

Compounds of formula (Ih), above, wherein the groups  $R_{11}$  and W have the values listed in Table 1, were prepared following the same or similar procedure described above for Example 1, using a different amino acid in place of N-Boc-L-histidine in Step A.

10

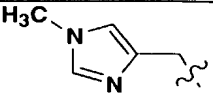

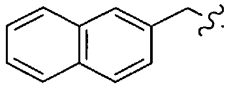

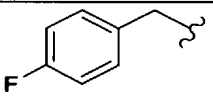

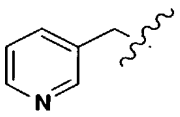

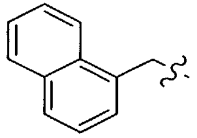

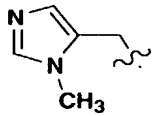

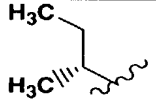

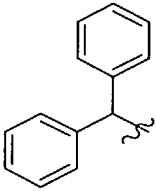

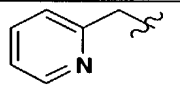

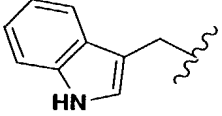

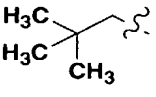

**TABLE 1**

Ex No.	$R_{11}$	W	Purity (%)	HPLC Ret. time (min)	Mass (M+H)
2			89	3.3	572.49
3	-CH <sub>3</sub>		90	3.2	480.46
4	-CH <sub>2</sub> -OH		89	3.2	496.49
5	-CH <sub>2</sub> CH <sub>3</sub>		85	3.2	494.49
6			92	3.0	522.33
7			90	3.2	510.45

HA0768NP

8			91	2.5	546.36
9			81	3.3	508.46
10			76	3.5	522.51
11			95	2.7	636.21
12			92	3.4	522.5
13			80	3.3	542.41
14			77	3.0	522.24
15			82	3.4	542.48
16			89	3.0	586.19
17			75	3.0	522.17
18			90	2.8	636.26
19			100	3.5	570.31

HA0768NP

20			92	2.5	560.39
21			87	3.2	606.23
22			96	3.0	574.22
23			95	2.5	557.3
24			96	3.7	606.32
25			94	2.5	560.15
26			87	2.9	522.26
27			93	3.7	632.32
28			76	2.8	557.13
29			81	3.2	612.2
30			88	3.1	536.29



HA0768NP

31	$-\text{CH}_3$		96	2.7	480.04
32			93	2.6	496.23
33			85	2.9	522.39
34			95	3.0	556.38
35	$-\text{CH}_3$		91	2.7	494.22
36			89	2.9	522.17
37			83	2.7	510.28
38			87	3.1	600.19
39			92	3.1	600.14
40			95	2.7	510.21
41			91	2.9	601.33
42			89	2.8	522.3
43			96	2.9	557.48

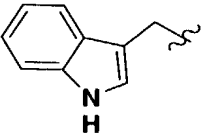

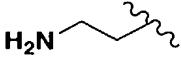

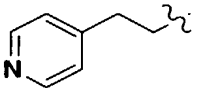


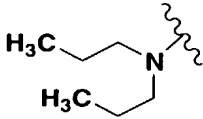
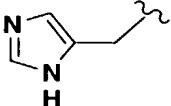

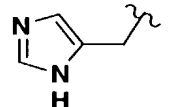
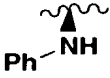


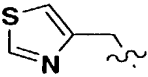


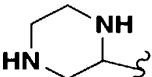
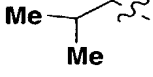
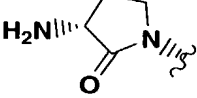
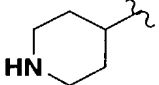
HA0768NP

44			89	3.1	590.09
45			96	2.5	523.22
46			76	3.2	624.07
47			82	2.9	570.14
48			79	3.7	630.33
49			86	3.1	633.88
50			90	3.0	582
51			96	3.1	590.23
52			87	3.2	590.06
53			82	3.1	587.87
54			89	3.0	574.28
55			91	2.9	557.47

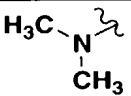
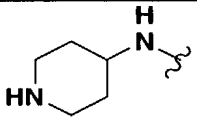
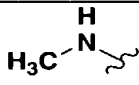
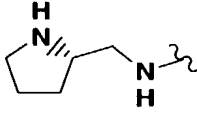
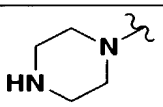
HA0768NP

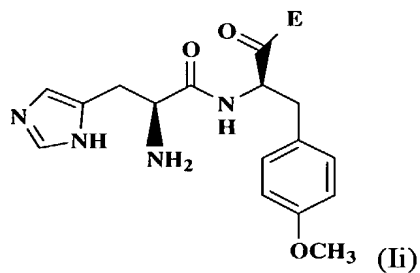
56	$-\text{CH}_3$		97	2.7	494.27
57			90	3.7	662.07
58			83	3.2	682.1
59			95	3.7	662.24
60			87	3.3	712.44
61			79	3.1	660.2
62			92	3.9	730
63			92	2.56	571.37
64			92	2.51	571.32
65			91	2.52	585.46
66			82	3.07	605
67			92	2.5	537.44

HA0768NP

68			90	4.3	595
69			91	2.48	509.33
70			94	2.51	571.35
71			94	2.9	564.44
72			93	2.71	547.28
73			93	2.71	636.35
74			93	2.47	495.29
75			88	2.79	563.23
76	H		90	3.1	466.46
77	H		89	2.54	535.33
78			82	3.07	605
79	H		91	2.76	534.33

HA0768NP

80	H		93	2.71	494.31
81	H		90	2.52	549.32
82	H		80	2.66	480.27
83	H		89	2.52	549.31
84	H		92	2.66	535.34

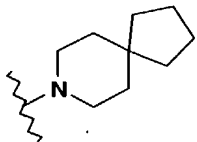
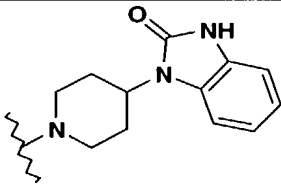
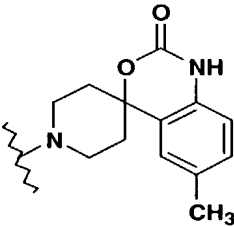
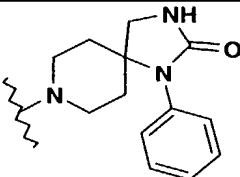
**EXAMPLES 85-88**

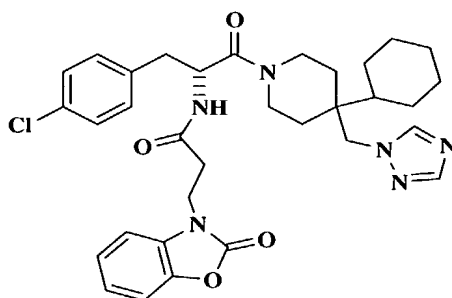
Compounds of formula (Ii), above, wherein the group E has the values shown in Table 2, were prepared following the same procedures as described above for Example 1.

**TABLE 2**

Ex. No.	E	Purity (%)	HPLC RT (min)	Mass (M+H)

HA0768NP

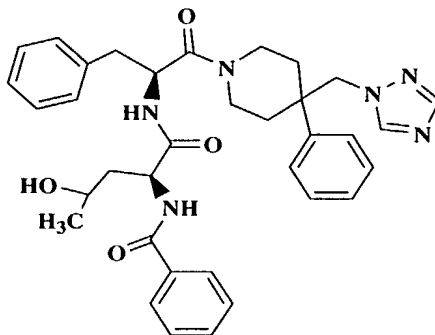
85		95	2.43	454
86		98	1.96	532
87		95	2.11	547
88		90	2.03	546

**EXAMPLE 89**

5

Example 89 was prepared following the same or similar procedure described  
 10 herein for Example 1. Purity 86.0%, HPLC ret. time = 3.1, MS (M+H)<sup>+</sup>=619.38.

HA0768NP

**EXAMPLE 90**

5

8

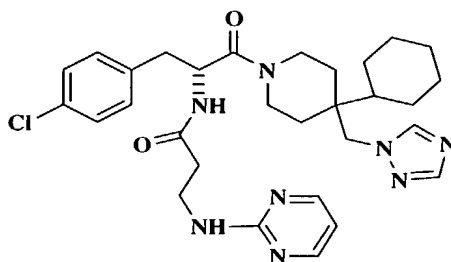
Example 90 was prepared following the same or similar procedure described herein for Example 1. Purity 93%, HPLC ret. time = 3.8 min, MS (M+H)<sup>+</sup> = 635.42.

10

**EXAMPLE 91**

N-[1-(4-Chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl)-piperidin-1-yl]-2-oxo-ethyl]-3-(pyrimidin-2-ylamino)-propionamide

15

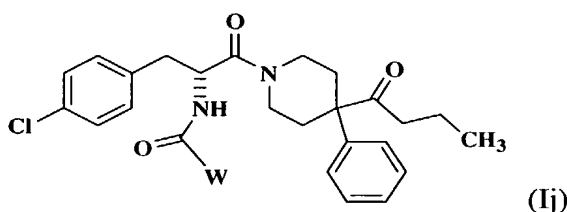


To a solution of Example 171 (35 mg, 0.07 mmol) and 2-bromopyrimidine (14 mg, 0.09 mmol) in EtOH (1.0 mL) at RT was added potassium carbonate (14 mg, 0.1 mmol). The mixture was heated to 60°C and stirred overnight at 60°C. The mixture was cooled to RT a sat'd solution of ammonium chloride (15 mL) was added. The separated aqueous layer was extracted with DCM (3 x 25 mL), and the combined organic layers were dried (MgSO<sub>4</sub> anh.), filtered, and evaporated to afford an oil (>80% purity by

20

HA0768NP

LCMS). The residue was purified using preparative HPLC and after evaporation, the residue was lyophilized to afford 32 mg (80% yield) of Example 91. This semi-solid was converted as its hydrochloride salt. HPLC/MS (A), ret. time = 1.68 min, purity 98.4%, MS pos.  $m/z$  579 (M+H)<sup>+</sup>; HPLC / MS (E), ret. time = 24.13 min, purity 97.4% <sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>)  $\delta$  ppm (two rotamers; 1:1.5 ratio) 8.45 (1H, s, minor rotamer), 8.44 (1H, s, major rotamer), 8.28 (2H, t, J = 4.6 Hz), 7.99 (1H, s, minor rotamer), 7.95 (1H, s, major rotamer), 7.31 (2H, d, J = 8.3 Hz, major rotamer), 7.27 (2H, d, J = 8.4 Hz, minor rotamer), 7.24 (2H, d, J = 8.6 Hz, major rotamer), 7.20 (2H, d, J = 8.4 Hz, minor rotamer), 6.63 (1H, t, J = 4.8 Hz), 5.09 (1H, m), 4.30 (2H, s, major rotamer), 4.26 (2H, s, minor rotamer), 3.64-3.45 (6H, m), 2.95 (2H, m), 2.52 (2H, m), 1.81-0.88 (15H, m).

**EXAMPLES 92-113**

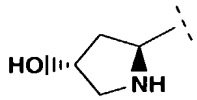
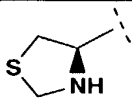
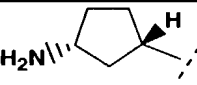
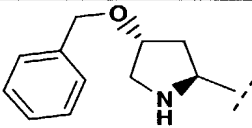
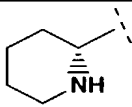
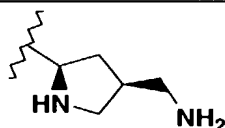
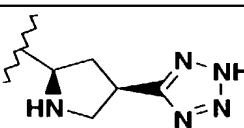
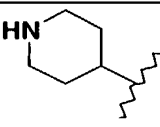
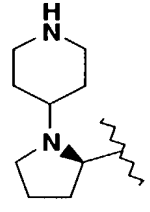
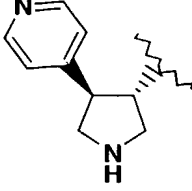
Compounds of formula (Ij), above, wherein the group W has the values listed in Table 3, were prepared following the same or similar procedure described above for Example 1, using a different amino acid in place of N-Boc-L-histidine in Step A.

**TABLE 3**

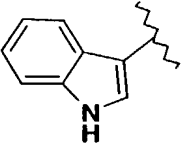
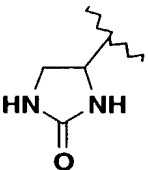
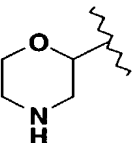
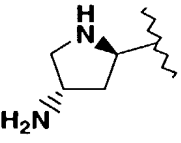
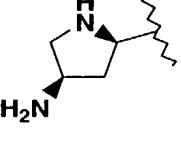
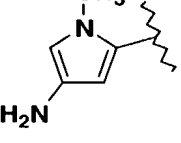
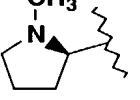
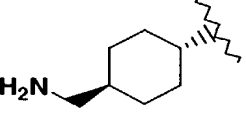
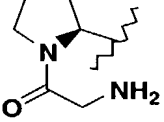
Ex. No.	W	Purity (%)	HPLC RT (min)	Mass (M+H)
92		87	3.2	506.5



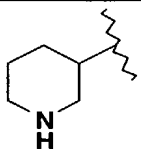
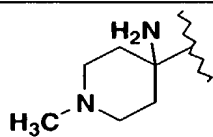
HA0768NP

93		91	3.2	522.45
94		81	3.1	524.23
95		82	2.8	520.25
96		94	3.0	612.28
97		96	2.7	520.43
98		92	2.5	535
99		85	2.72	574
100		93	2.73	520.41
101		93	2.56	589.52
102		96	2.54	583.38

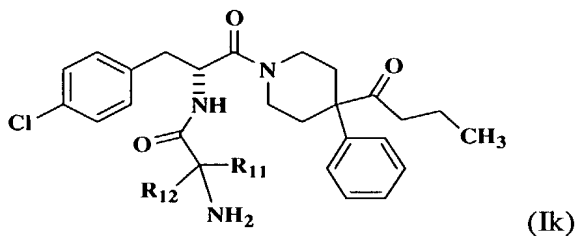
HA0768NP

103		96	2.95	554.28
104		85	4.31	521
105		79	2.73	522.3
106		91	2.52	521.33
107		92	2.5	521.33
108		80	2.82	531.28
109		94	2.72	520.36
110		86	2.8	548.34
111		86	2.8	563.27

HA0768NP

112		80	2.74	520.33
113		92	2.49	549.33

**EXAMPLES 114-115**




5

Compounds of formula (Ik), above, wherein the groups  $R_{11}$  and  $R_{12}$  have the values listed in Table 4, were prepared following the same or similar procedure described above for Example 1, using a different amino acid in place of N-Boc-L-histidine in Step

10 A.

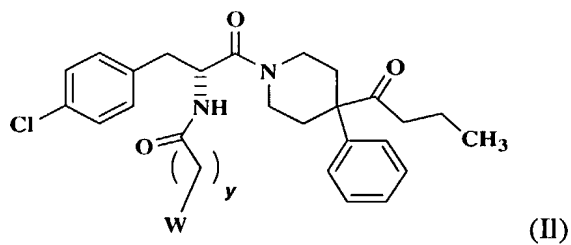
**TABLE 4**

Ex. No.	$R_{11}$	$R_{12}$	Purity (%)	HPLC RT (min)	Mass (M+H)
114	-CH <sub>3</sub>	-CH <sub>3</sub>	92	3.2	494.49
115			95	2.7	492.25

**EXAMPLES 116-117**

15

HA0768NP



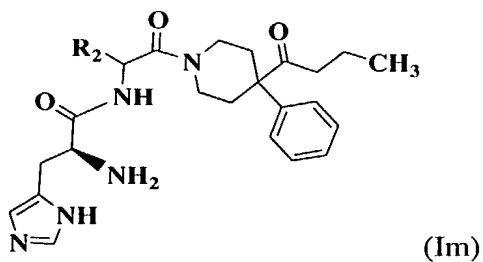
Compounds of formula (II), above, wherein the integer  $y$  and group  $W$  have the values listed in Table 5, were prepared following the same or similar procedure described above for Example 1, using a different amino acid in place of N-Boc-L-histidine in Step A.

TABLE 5

Ex. No.	$y$	W	Purity (%)	HPLC RT (min)	Mass (M+H)
116	2		96	2.79	548.34
117	4		95	2.74	536.36

EXAMPLES 118-157

HA0768NP



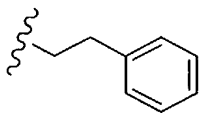
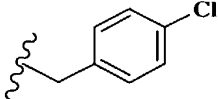
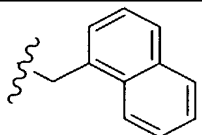
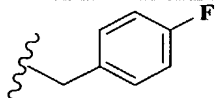
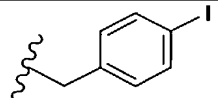
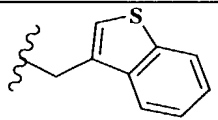
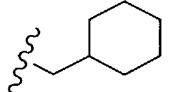
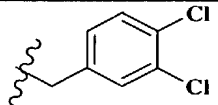
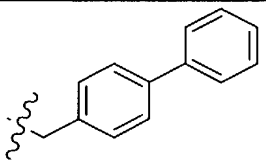
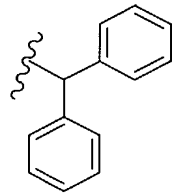
Compounds of formula (Im), above, wherein R<sub>2</sub> has the values listed in Table 6, were prepared following the same procedure described for Example 1, except a different

5 methyl ester hydrochloride was used in place of methoxyphenylalanine methyl ester hydrochloride in Step A.

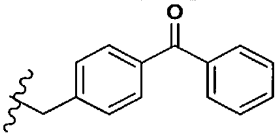
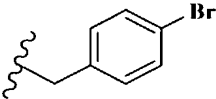
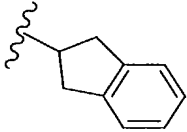
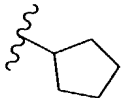
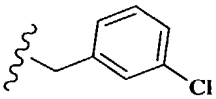
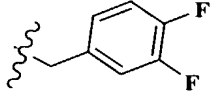
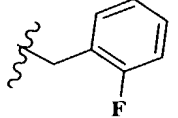
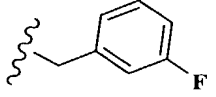
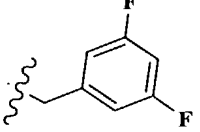
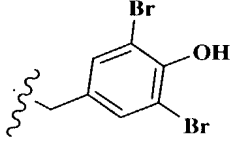
**TABLE 6**

Ex. No.	R <sub>2</sub>	Purity (%)	HPLC RT (min)	Mass (M+H)
118		76	3.0	482.36
119		74	2.9	502.35
120		75	3.0	482.36
121		87	3.0	522.32
122		86	3.0	561.3
123		93	3.3	566.33

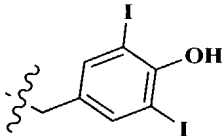
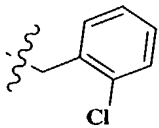
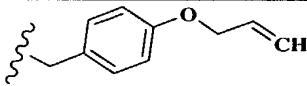
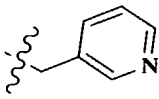
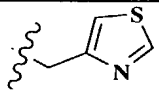
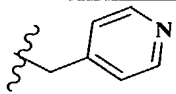
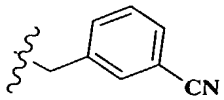
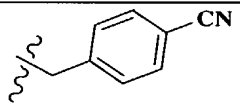
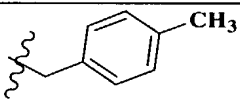
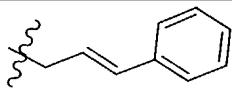
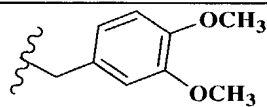
HA0768NP

124		78	3.2	530.37
125		89	3.2	550.29
126		85	3.3	566.34
127		84	3.1	534.35
128		78	3.3	642.24
129		88	3.3	572.32
130		87	3.3	522.43
131		90	3.4	584.26
132		89	3.5	592.38
133		90	3.3	592.38

HA0768NP

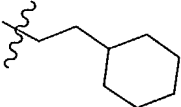
134		84	3.2	620.38
135		92	3.3	594.25
136		88	3.2	542.36
137		93	3.0	494.36
138		92	3.2	550.29
139		84	3.1	552.31
140		79	3.0	534.34
141		78	3.1	534.36
142		76	3.1	552.33
143		89	3.0	690.16

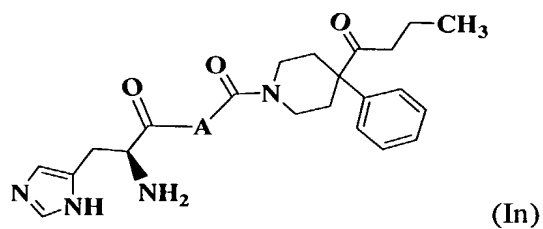
HA0768NP

144		93	3.1	784.11
145		93	3.1	550.32
146		84	3.2	572.38
147		88	2.3	517.4
148		79	2.7	523.35
149		90	2.3	517.4
150		84	2.8	541.38
151	H	84	2.5	426.35
152	-CH <sub>3</sub>	85	2.5	440.35
153		85	2.8	541.36
154		73	3.2	530.41
155		83	3.2	542.4
156		89	2.8	576.4



HA0768NP

157		77	3.5	536.46
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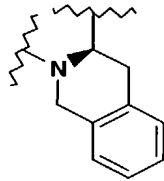
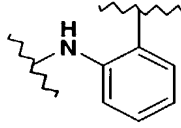
**EXAMPLES 158-167**

5

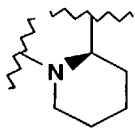
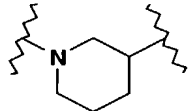
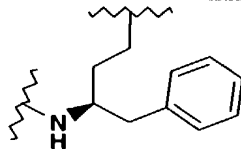
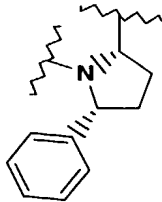
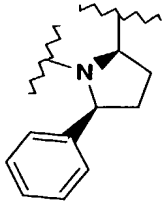
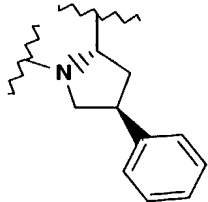
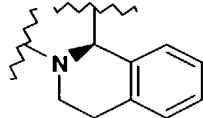
Compounds of formula (In), above, wherein A has the values listed in Table 7 { wherein in compounds of formula (I),  $A = X(R_1)-CH(R_2)-CH(R_3)_r-(CH_2)_s-$  }, were prepared following the same procedure described for Example 1, except a different methyl ester hydrochloride was used in place of methoxyphenylalanine methyl ester hydrochloride in Step A.

10

**TABLE 7**

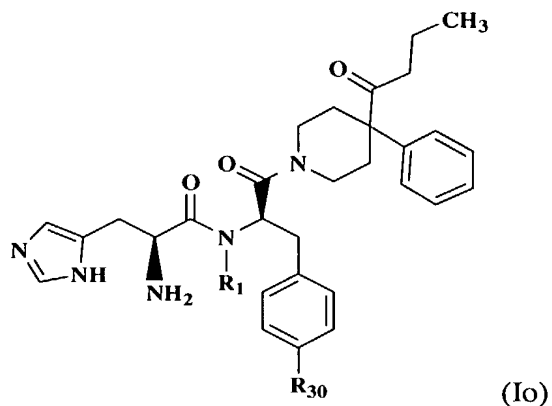
Ex. No.	A	Purity (%)	HPLC RT (min)	Mass (M+H)
158	$-CH_2CH_2-$	82	2.6	440.32
159		73	2.9	528.37
160		88	2.8	488.33

HA0768NP

161		71	2.8	480.34
162		84	2.7	480.36
163		89	3.1	544.39
164		85	3.0	542.38
165		74	3.1	542.39
166		90	3.1	542.4
167		83	3.0	528.39

**EXAMPLES 168-170**

HA0768NP

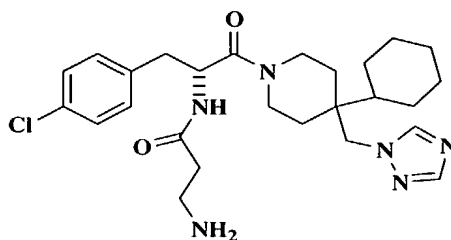


Compounds of formula (Io), above, wherein the groups  $R_1$  and  $R_{30}$  have the values listed in Table 8, were prepared following the same procedure as for Example 1, except a different methyl ester hydrochloride was used in Step A.

**TABLE 8**

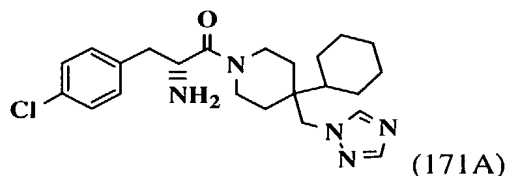
Ex. No.	$R_1$	$R_{30}$	Purity (%)	HPLC RT (min)	Mass (M+H)
168	H	Cl	90	3.08	551
169	H	H	86	2.88	515
170	CH <sub>3</sub>	Cl	85	3.26	565

10

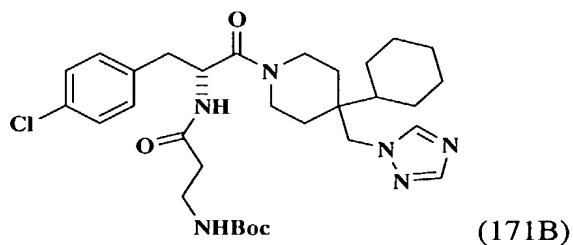
**EXAMPLE 171**

15

HA0768NP

Step A:

Compound 171A was prepared by coupling of commercially available N-BOC D-4-chlorophenylalanine and 4-Cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidine , followed by deprotection of the BOC group, as described in WO 00/74679, incorporated herein by reference.

Step B:

To a solution of  $\alpha$ -amino amide from step A (1.1 g, 2.56 mmol) and N-Boc- $\beta$ -alanine (531 mg, 2.81 mmol) in DCM (12 mL) was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (736 mg, 3.8 mmol) and HOBt (518 mg, 3.8 mmol) at RT. The mixture was stirred at RT overnight and a sat'd solution of ammonium chloride (15 mL) was added. The separated aqueous layer was extracted with DCM (3 x 25 mL), and the combined organic layers were dried (MgSO<sub>4</sub> anh.), filtered, and evaporated to afford compound 171A which was used in the next step without purification.

Step C:

## Example 171

To a solution of Compound 171B (1.0 g, 1.7 mmol) in DCM (10 mL) was added a 20% (v/v) solution of TFA in DCM (1.6 mL) at RT. The mixture was stirred at RT for 8 h and evaporated under reduced pressure. The residue was purified using preparative

HA0768NP

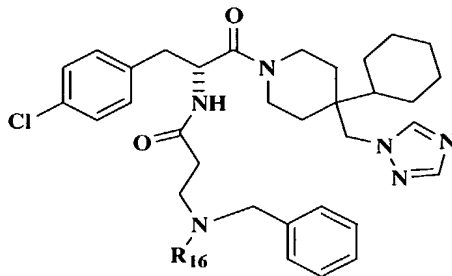
HPLC and after evaporation, the residue was lyophilized to afford 0.9 g (47% yield) of Example 171 as the TFA salt. HPLC/MS (A), ret. time = 1.50 min, purity 86.9%, MS pos.  $m/z$  501 ( $M+H$ )<sup>+</sup>; HPLC/MS (E), ret. time = 10.81 min, purity 100%; ir ( $\nu_{\max}$ , KBr)  $\text{cm}^{-1}$  3600-2880, 1695, 1620; <sup>1</sup>H NMR (400 MHz, MeOH- $d_4$ )  $\delta$  ppm (two rotamers; 1:2 ratio) 8.43 (1H, s, minor rotamer), 8.42 (1H, s, major rotamer), 7.96 (1H, s, minor rotamer), 7.92 (1H, s, major rotamer), 7.26 (2H, d,  $J$  = 8.3 Hz, major rotamer), 7.23 (2H, d,  $J$  = 8.4 Hz, minor rotamer), 7.18 (2H, d,  $J$  = 8.3 Hz, major rotamer), 7.15 (2H, d,  $J$  = 8.6 Hz, minor rotamer), 4.98 (1H, t,  $J$  = 7.8 Hz), 4.21 (2H, s, major rotamer), 4.18 (2H, s, minor rotamer), 3.60 (1H, m), 3.31 (3H, m), 3.08 (2H, m), 2.87 (2H, m), 2.54 (2H, t,  $J$  = 6.5 Hz), 1.95-0.82 (15H, m). *Anal.* Calc'd for  $\text{C}_{26}\text{H}_{37}\text{ClN}_6\text{O}_2 \cdot 3\text{CF}_3\text{COOH} \cdot 2\text{H}_2\text{O}$ : C, 43.72; H, 5.04; N, 9.56. Found: C, 43.90; H, 4.31; N, 9.16. *Anal.* Calc'd for  $\text{C}_{26}\text{H}_{37}\text{ClN}_6\text{O}_2 \cdot 3\text{HCl} \cdot \text{H}_2\text{O}$ : C, 49.69; H, 6.74; N, 13.37. Found: C, 49.96; H, 6.75; N, 12.88.

15

### EXAMPLES 172 AND 173

3-Benzylamino-N-[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-propionamide (Ex. 172), and 3-diBenzylamino-N-[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-propionamide (Ex. 173)

20



Example 172:  $R_{16} = \text{H}$

Example 173:  $R_{16} = \text{Bz}$

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At RT, benzaldehyde (13  $\mu$ L, 0.13 mmol) was added to a solution of Example 171 (48.5 mg, 0.1 mmol) in DCE (1 mL). Sodium triacetoxymethylborohydride (29 mg, 0.14 mmol) was added, the mixture was stirred at RT for 24 hours, and a sat'd solution of ammonium chloride (15 mL) was added. The separated aqueous layer was extracted with DCM (3 x 25 mL) and the combined organic layers were dried ( $\text{MgSO}_4$  anh.), filtered, and evaporated to afford 36 mg of an oil which consisted in a (11:1) mixture of Examples 172 and 173, as determined by HPLC/MS. The purification was performed using preparative (Column: Premisphere 5 $\mu$ -C8 21 x 100 mm) HPLC (acetonitrile-5 mM  $\text{NH}_4\text{OAc}$ /water: 7 min. gradient from 50% AcCN to 90% AcCN at 220 nm. Flow rate: 20 mL/min.), and after evaporation, the residue was lyophilized to afford 24 mg (42% yield) of Ex. 172 along with 6 mg (9% yield) of Ex. 173.

**Ex. 172:** HPLC / MS (Column: Premisphere- C18 4.6 x 30 mm; Flow rate: 4 mL / min, Solvent system: 0-100% B in 2 min. Solvent A: 10%  $\text{CH}_3\text{CN}$  - 90 % $\text{H}_2\text{O}$  – 5mM  $\text{NH}_4\text{OAc}$ ; Solvent B: 90%  $\text{CH}_3\text{CN}$  - 10 % $\text{H}_2\text{O}$  – 5mM  $\text{NH}_4\text{OAc}$ ; UV: 220 nm; Micromass ZMD 2000, ESI): retention time 1.76 min, purity 100%, MS pos.  $m/z$  591 ( $\text{M}+\text{H}$ )<sup>+</sup>; HPLC / MS (Column: YMC ODS-A C18 4.6 x 150 mm; Flow rate: 1 mL / min, Solvent system: 30-100% B in 30 min., UV: 220 nm;): retention time 12.13 min, purity 100%  $^1\text{H}$  nmr (400 MHz,  $\text{MeOH}-d_4$ )  $\delta$  ppm (two rotamers; 1:1.5 ratio) 8.47 (1H, s, minor rotamer), 8.45 (1H, s, major rotamer), 8.02 (1H, s, minor rotamer), 7.97 (1H, s, major rotamer), 7.41 (5H, m), 7.34 (2H, d,  $J$  = 8.4 Hz, major rotamer), 7.30 (2H, d,  $J$  = 8.3 Hz, minor rotamer), 7.27 (2H, d,  $J$  = 8.3 Hz, major rotamer), 7.23 (2H, d,  $J$  = 8.6 Hz, minor rotamer), 5.09 (1H, br. t,  $J$  = 6.8 Hz), 4.31 (2H, s, major rotamer), 4.29 (2H, s, minor rotamer), 4.00 (2H, s, major rotamer), 3.96 (2H, s, minor rotamer), 3.75-3.36 (4H, m), 3.00 (4H, m), 2.57 (2H, t,  $J$  = 6.8 Hz), 1.80-0.89 (15H, m).

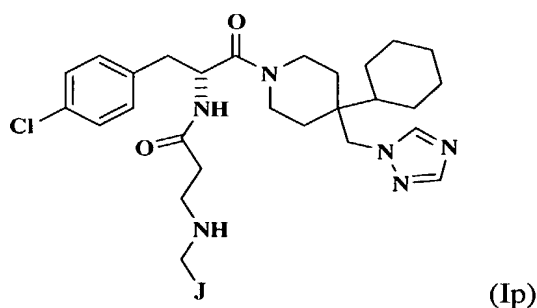
**Ex. 173:** HPLC / MS (Column: Premisphere- C18 4.6 x 30 mm; Flow rate: 4 mL / min, Solvent system: 0-100% B in 2 min. Solvent A: 10%  $\text{CH}_3\text{CN}$  - 90 % $\text{H}_2\text{O}$  – 5mM  $\text{NH}_4\text{OAc}$ ; Solvent B: 90%  $\text{CH}_3\text{CN}$  - 10 % $\text{H}_2\text{O}$  – 5mM  $\text{NH}_4\text{OAc}$ ; UV: 220 nm;

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Micromass ZMD 2000, ESI): retention time 2.45 min, purity 96.7%, MS pos.  $m/z$  681  
 (M+H)<sup>+</sup>; <sup>1</sup>H nmr (400 MHz, MeOH-d<sub>4</sub>)  $\delta$  ppm (two rotamers present; 1:1.4 ratio) 8.46  
 (1H, s, minor rotamer), 8.42 (1H, s, major rotamer), 8.01 (1H, s, minor rotamer), 7.93  
 (1H, s, major rotamer), 7.43-7.10 (14H, m), 5.10 (1H, m), 4.30 (2H, s, major rotamer),  
 5 4.28 (2H, s, minor rotamer), 3.77 (1H, m), 3.70 (2H, s, minor rotamer), 3.66 (2H, s, major  
 rotamer), 3.66-3.36 (7H, m), 3.01-2.35 (5H, m), 1.90-0.79 (15H, m).

**EXAMPLES 174-186**

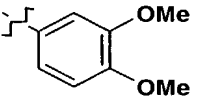
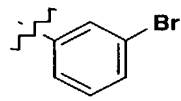
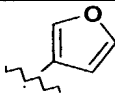
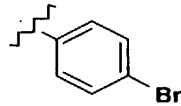
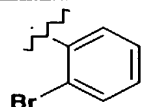
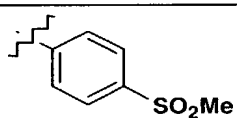
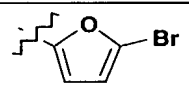
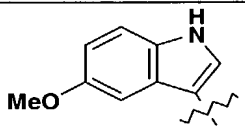
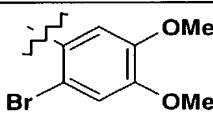
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15 Compounds of formula (Ip), above, wherein the group J has the values listed in  
 Table 9, were prepared following the same procedure described for Examples 175-76,  
 using with different aldehydes in place of benzaldehyde.

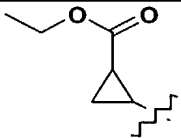
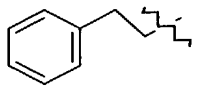
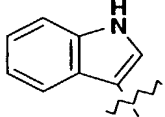
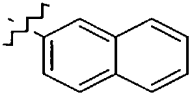
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TABLE 9

Ex. No.	J	HPLC Retention Time (min) <sup>b</sup>	MS Data <sup>b</sup> (M + H) <sup>+</sup>
174		1.84	650
175		2.08	668
176		1.80	580
177		2.07	668
178		2.05	668
179		1.75	668
180		1.96	660
181		1.91	659
182		1.97	730



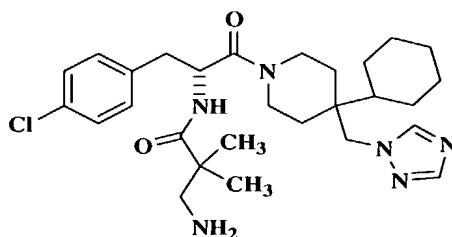
HA0768NP

183		1.84	626
184		2.00	618
185		1.92	629
186		2.11	640

**EXAMPLE 187**

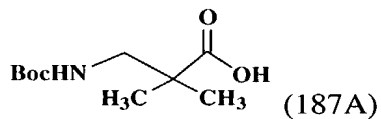
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3-Amino-N-[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-2,2-dimethyl-propionamide



10

Step A:



15

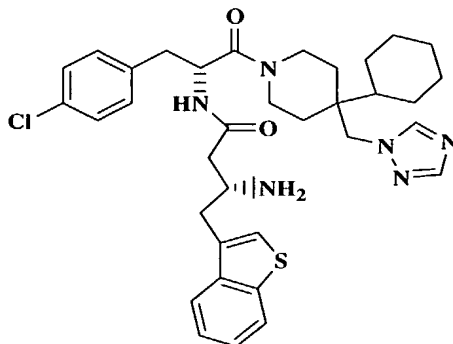
Compound 187A was prepared following the procedure described in Dhokte et al., *Tetrahedron Lett.*, Vol. 39 (1998), at pp. 8771-8774.

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## Step B:

Example 187 was prepared following the procedure described for the preparation of Example 171, using Compound (187A) in place of Boc- $\beta$ -alanine in Step A.

- 5 HPLC/MS (F), ret. time 1.64 min, purity 95.7%, MS pos.  $m/z$  529 (M+H)<sup>+</sup>; HPLC / MS (H), ret. time = 12.12 min, purity 95.1%; <sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>)  $\delta$ ppm (two rotamers; 1:1.4 ratio) 8.56 (1H, s, minor rotamer), 8.53 (1H, s, major rotamer), 8.08 (1H, s, minor rotamer), 8.02 (1H, s, major rotamer), 7.36 (2H, d, J = 8.4 Hz, major rotamer), 7.34 (2H, d, J = 8.9 Hz, minor rotamer), 7.28 (2H, d, J = 8.3 Hz, major rotamer), 7.25 (2H, d, J = 8.4 Hz, minor rotamer), 5.07 (1H, m), 4.32 (2H, s), 3.68-3.34 (4H, m), 3.02 (4H, m), 1.98-0.99 (15H, m), 1.34, 1.24 (6H, 2s, minor rotamer), 1.33, 1.28 (6H, 2s, major rotamer).

**EXAMPLE 188**

Example 188 was prepared using the same procedure as described for the

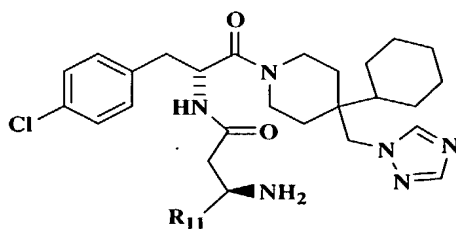
- 20 preparation of Example 171, starting with  $\beta$ -amino acid . HPLC / MS (E), ret. time = 2.04 min, purity 98.7%, MS pos.  $m/z$  647 (M+H)<sup>+</sup>; HPLC (G), ret. time = 2.75 min, purity 94.8%; MS (Finigan TSQ 7000, ESI)  $m/z$  647 (M+H)<sup>+</sup>; HRMS calculated for C<sub>35</sub>H<sub>43</sub>ClN<sub>6</sub>O<sub>2</sub>S: 647.2925, found: 647.2935 <sup>1</sup>H NMR (400 MHz, MeOH-

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d<sub>4</sub>)  $\delta$  ppm (two rotamers; ratio 1.6:1) 8.71 (1H, s, minor rotamer), 8.64 (1H, s, major rotamer), 8.16 (1H, s, minor rotamer), 8.07 (1H, s, major rotamer), 7.93 (1H, d,  $J = 8$  Hz), 7.82 (1H, t,  $J = 8$  Hz), 7.48-7.38 (3H, m), 7.26 (2H, d,  $J = 8$  Hz), 7.19 (2H, d,  $J = 8$  Hz), 7.18 (1H, d,  $J = 8$  Hz), 5.03-4.95 (1H, m), 4.29 (2H, s), 4.18 (1H, m), 4.12 (1H, m), 3.92-3.75 (1H, m), 3.69-3.59 (4H, m), 3.51-3.35 (1H, m), 3.20-3.06 (2H, m), 2.98-2.80 (2H, m), 2.63-2.48 (2H, m), 1.85-0.85 (14H, m).

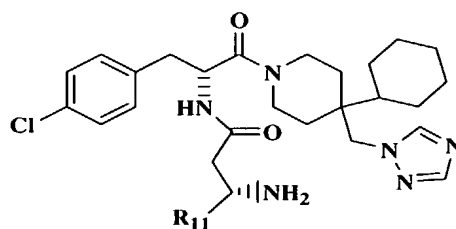
**EXAMPLES 189-217**

10



Core A

(Iq)



Core B

Compounds having the formula (Iq), and Core A and B as noted in Table 10, wherein  $R_{11}$  has the values listed in Table 10, were prepared using the same procedure described above for the preparation of Example 171 starting with the appropriately substituted  $\beta$ -

amino acid  $\text{HOOC}-\text{CH}(\text{BocHN})-\text{CH}_2-\text{R}_{11}$ . The compounds were prepared via high-throughput synthesis. The crude product was purified either by automated SPE-SCX using a Zymark BenchMate Workstation or Shimadzu automated preparative HPLC system and concentrated *in vacuo*. The SPE workstation was carried out as follows:

- 1) Conditioned a SPE column (SCX cation exchange, 1.5 g of sorbent, 0.79 mequiv / g) with 10 mL of methanol (0.25 mL / sec) and 10 mL of a 1:1 mixture methanol /  $\text{H}_2\text{O}$ ;
- 2) Loaded reaction contents onto the column (0.05 mL / sec);
- 3) Washed column with 2 x 10 mL of methanol (0.20 mL / sec);
- 4) Eluted column with 2 x 8 mL of 2M ammonia in methanol and collected the effluent into a tared receiving tube (0.10 mL / sec); and

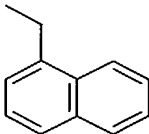
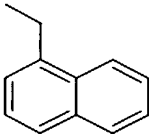
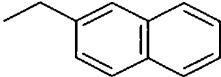
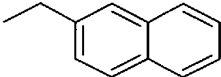
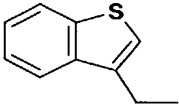
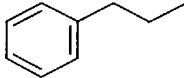
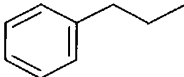
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5) Concentrated the products using a Savant Speedvac Plus SC210A.

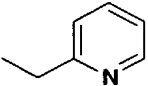

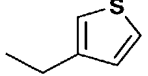
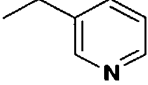

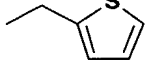
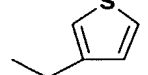
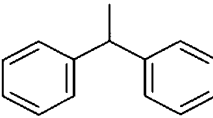
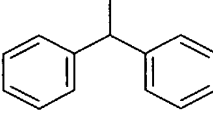
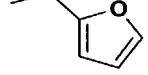
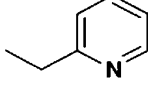
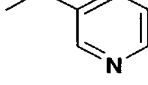
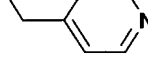
Compounds purified by preparative HPLC were diluted in MeOH (2 mL) and purified using a Shimadzu LC-10A automated preparative HPLC system and the following conditions: initial gradient (80 % A, 20 % B) ramp to final gradient (0 % A, 100 % B) over 8 min., hold for 4 min. (0 % A, 100 % B), Solvent A: 10 % AcCN / 90 % H<sub>2</sub>O / 5mM NH<sub>4</sub>OAc, Solvent B: 90 % AcCN / 10 % H<sub>2</sub>O / 5mM NH<sub>4</sub>OAc, Column Primesphere C18-HC 21.2 x 100 mm, Detector Wavelength: 220 nm.

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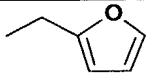
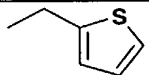
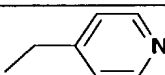
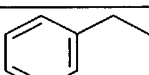
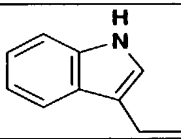
**TABLE 10**

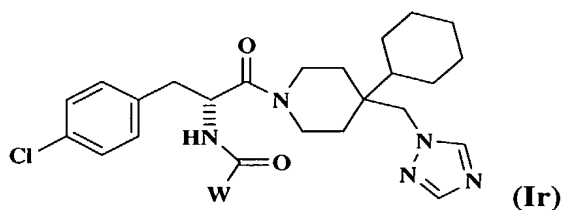
Ex.	Core	R <sub>11</sub>	HPLC Retention Time (min)	MS Data (M + H) <sup>+</sup>
189	B		3.28 <sup>c</sup>	641
190	A		3.21 <sup>c</sup>	641
191	B		3.28 <sup>c</sup>	641
192	A		3.22 <sup>c</sup>	641
193	B		3.28 <sup>c</sup>	647
194	B		1.70 <sup>b</sup>	605
195	A		1.67 <sup>b</sup>	605

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196	B		1.37 <sup>b</sup>	592
197	A		1.57 <sup>b</sup>	577
198	A		1.60 <sup>b</sup>	597
199	B		1.38 <sup>b</sup>	592
200	B		1.59 <sup>b</sup>	577
201	B		1.60 <sup>b</sup>	597
202	B		1.62 <sup>b</sup>	597
203	B		1.97 <sup>b</sup>	667
204	A		1.77 <sup>b</sup>	667
205	B		1.14 <sup>b</sup>	581
206	A		0.44 <sup>b</sup>	592
207	A		0.39 <sup>b</sup>	592
208	B		0.30 <sup>b</sup>	592

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209	A		1.27 <sup>b</sup>	581
210	A		1.51 <sup>b</sup>	597
211	A		0.94 <sup>b</sup>	592
212	A		1.56 <sup>b</sup>	591
213	A	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> -	1.79 <sup>a</sup>	557
214	A	(CH <sub>3</sub> ) <sub>2</sub> CH-	1.71 <sup>a</sup>	543
215	A	(S)-(C <sub>2</sub> H <sub>5</sub> )(CH <sub>3</sub> )C <sup>*</sup> H-	1.76 <sup>a</sup>	557
216	A		1.84 <sup>a</sup>	630
217	A	CH <sub>3</sub> -	1.62 <sup>a</sup>	515

**EXAMPLES 218-237**

5

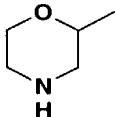
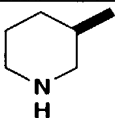
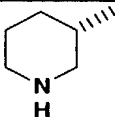
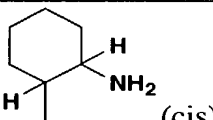
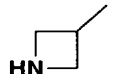
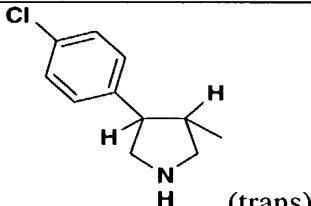
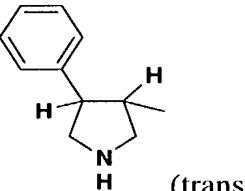
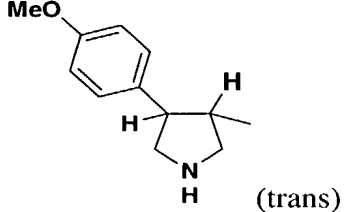
Compounds having the formula (Ir), wherein W has the values listed in Table 11, were prepared using the same or similar procedure described above for the preparation of

10 Examples 187-197.

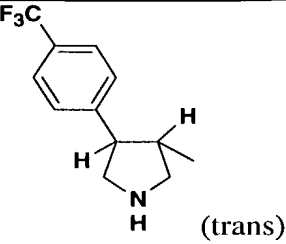
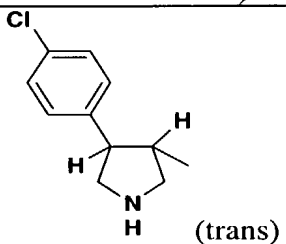
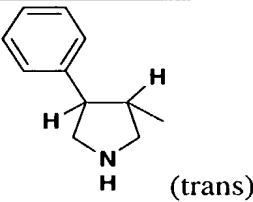
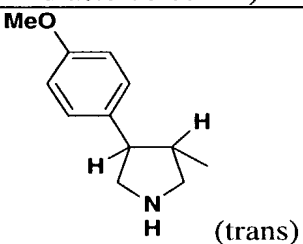
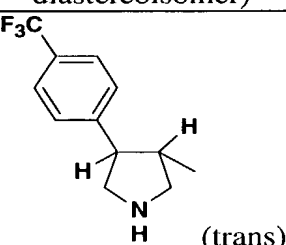
**TABLE 11**

x.	W	HPLC Ret. Time (min)	MS Data (M + H) <sup>+</sup>
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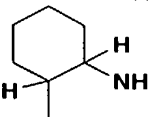
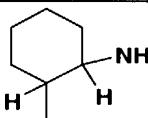
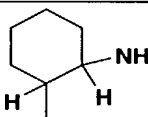


218		1.72 <sup>a</sup>	543
219		1.72 <sup>a</sup>	541
220		1.65 <sup>a</sup>	541
221	 (cis) (less polar diastereoisomer)	1.91 <sup>a</sup>	555
222		1.65 <sup>a</sup>	513
223	 (trans) (more polar diastereoisomer)	1.94 <sup>a</sup>	637
224	 (trans) (more polar diastereoisomer)	1.82 <sup>a</sup>	603
225	 (trans) (more polar diastereoisomer)	1.82 <sup>a</sup>	633

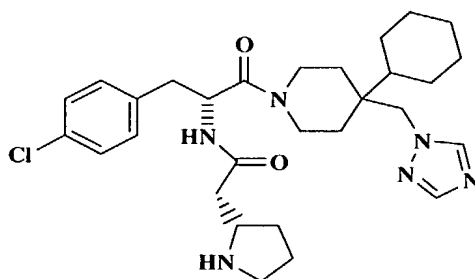
HA0768NP

226	 <p>(trans) (more polar diastereoisomer)</p>	1.99 <sup>a</sup>	671
227	 <p>(trans) (less polar diastereoisomer)</p>	2.07 <sup>a</sup>	637
228	 <p>(trans) (less polar diastereoisomer)</p>	1.94 <sup>a</sup>	603
229	 <p>(trans) (less polar diastereoisomer)</p>	1.91 <sup>a</sup>	633
230	 <p>(trans) (less polar diastereoisomer)</p>	2.09 <sup>a</sup>	671



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231	 (cis) (more polar diastereoisomer)	1.74 <sup>a</sup>	555
232	 (trans) (less polar diastereoisomer)	1.67 <sup>a</sup>	555
233	 (trans) (more polar diastereoisomer)	1.80 <sup>a</sup>	555
234	CH <sub>3</sub> NHCH <sub>2</sub> –	1.83 <sup>a</sup>	501
235		1.89 <sup>a</sup>	513
236		1.82 <sup>a</sup>	513
237	(CH <sub>3</sub> ) <sub>2</sub> NCH <sub>2</sub> –	1.84 <sup>a</sup>	515

**EXAMPLE 238**

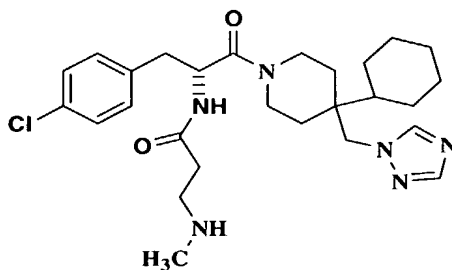
5

Example 238 was prepared following the same procedure described above for Examples 217-237. HPLC (A), ret. time = 1.77, (M+S)<sup>+</sup>=541.

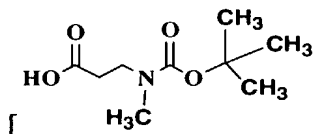
HA0768NP

**EXAMPLE 239**

N-[1-(4-Chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-3-methylamino-propionamide



To a solution of Compound 171A (80 mg, 0.19 mmol) and carbamate



[ (45 mg, 0.22 mmol) in DCM was added EDCI (57 mg, 0.3 mmol) and HOBt (40 mg, 0.3 mmol). The mixture was stirred at RT overnight and a sat'd solution of ammonium chloride (15 mL) was added. The separated aqueous layer was extracted with DCM (3 x 25 mL), and the combined organic layers were dried (MgSO<sub>4</sub> anh.), filtered and evaporated to afford a *tert*-butylcarbamate intermediate. The *tert*-butylcarbamate intermediate was dissolved in DCM (10 mL), and a 20% (v/v) solution of TFA in DCM (1.6 mL) was added at RT. The mixture was stirred at RT for 8 hours and evaporated under reduced pressure. The residue was purified using HPLC and after evaporation, the residue was lyophilized to afford Example 239 as the TFA salt. HPLC / MS (J), ret. time = 1.66 min, purity 100% .Micromass ZMD 2000, ESI): MS pos. *m/z* 515 (M+H)<sup>+</sup> ; HPLC (H), ret. time = 18.78, 19.15 min, purity 93.1%). <sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>) δ ppm (two rotamers; 1:1.7 ratio) 8.55 (1H, s, minor rotamer), 8.54 (1H, s, major rotamer), 8.08 (1H, s, minor rotamer), 8.03 (1H, s, major rotamer), 7.35 (2H, d, J = 8.3 Hz, major rotamer), 7.29 (2H, d, J = 8.4 Hz, minor rotamer), 7.28 (2H, d, J = 8.3 Hz,

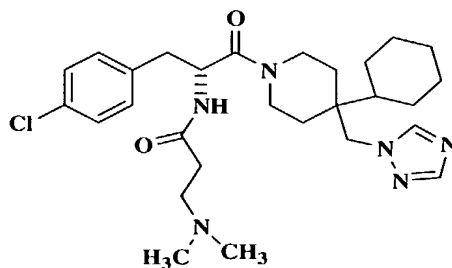
HA0768NP

major rotamer), 7.26 (2H, d, J = 8.6 Hz, minor rotamer), 5.08 (1H, t, J = 7.8 Hz), 4.32 (2H, s, major rotamer), 4.29 (2H, s, minor rotamer), 3.60 (1H, m), 3.31 (3H, m), 3.08 (2H, m), 2.87 (2H, m), 2.54 (5H, m), 1.95-0.82 (15H, m).

5

**EXAMPLE 240**

N-[1-(4-Chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-3-dimethylamino-propionamide



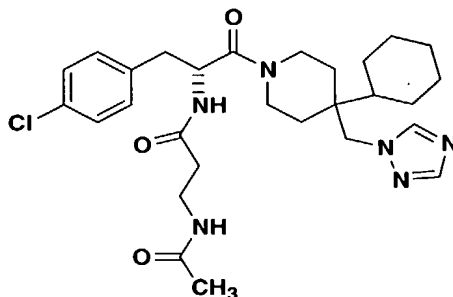
10

To a vigorously stirred solution of Example 171 (45 mg, 0.09 mmol) and formaldehyde (37% w/w in water, 45  $\mu$ L, 0.5 mmol) in DCE (1.0 mL) was added sodium triacetoxyborohydride (110 mg, 0.5 mmol) at RT. The mixture was stirred overnight at  
 15 RT and a sat'd solution of ammonium acetate (5 mL) was added. The separated aqueous layer was extracted with methylene chloride (3 x 15 mL), and the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated under reduced pressure. The residue was purified using preparative HPLC and after evaporation, the residue was lyophilized to afford Example 240 as the TFA salt. HPLC / MS (A), ret. time = 1.74 min, purity  
 20 98.2% Micromass ZMD 2000, ESI): MS pos.  $m/z$  529 ( $\text{M}+\text{H}$ )<sup>+</sup>; HPLC (K), ret. time = 19.58 min, purity 84.3%. <sup>1</sup>H NMR (400 MHz,  $\text{MeOH-d}_4$ ),  $\delta$  ppm (two rotamers; 1:1.7 ratio) 8.56 (1H, s, minor rotamer), 8.53 (1H, s, major rotamer), 8.08 (1H, s, minor rotamer), 8.03 (1H, s, major rotamer), 7.35 (2H, d, J = 8.3 Hz, major rotamer), 7.29 (2H, d, J = 8.4 Hz, minor rotamer), 7.28 (2H, d, J = 8.3 Hz, major rotamer), 7.26 (2H, d, J =  
 25 8.6 Hz, minor rotamer), 5.00 (1H, m), 4.31 (2H, m), 3.70-2.85 (11H, m), 2.92 (6H, br. s), 2.74 (2H, m), 1.91-0.75 (15H, m).

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**EXAMPLE 241**

3-Acetylamino-N-[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-propionamide

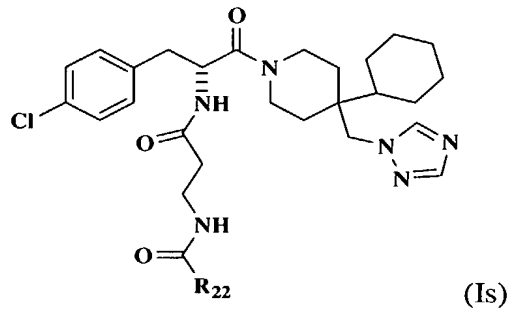


5

Acetyl chloride (25  $\mu$ L, 3.3 mmol) was added to a solution of Example 171 (150 mg, 3.0 mmol) and Et<sub>3</sub>N (50  $\mu$ L, 3.6 mmol) in DCM (7 mL) at 0°C. The mixture was stirred at RT overnight and quenched with sat'd ammonium chloride (10 mL). The separated aqueous layer was extracted with methylene chloride (3 x 15 mL), and the combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated under reduced pressure. The residue was purified using preparative HPLC, and after evaporation, the residue was lyophilized to afford Example 241 as the TFA salt. HPLC / MS (A?), ret. time = 1.60 min, purity 91.6%. Micromass ZMD 2000, ESI: MS pos.  $m/z$  543 (M+H)<sup>+</sup>; HPLC (K), ret. time = 20.98 min, purity 92.6%. <sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>)  $\delta$  ppm (two rotamers; 1:1.6 ratio) 8.56 (1H, s), 8.13 (1H, s), 7.35 (2H, d, J = 8.1 Hz, major rotamer), 7.30 (2H, d, J = 8.1 Hz, minor rotamer), 7.28 (2H, d, J = 8.1 Hz, major rotamer), 7.24 (2H, d, J = 8.6 Hz, minor rotamer), 5.08 (1H, br. t, J = 3.3 Hz), 4.34 (2H, s, major rotamer), 4.29 (2H, s, minor rotamer), 3.70-2.85 (11H, m), 2.74 (2H, m), 1.96 (3H, s, major rotamer), 1.94 (3H, s, minor rotamer), 1.91-0.75 (15H, m).

20

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**EXAMPLES 242-251**

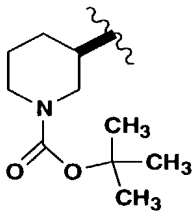
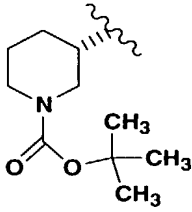
- 5            Compounds having the formula (Is), wherein R<sub>22</sub> has the values listed in Table 12, were prepared using EDCI-HOBt coupling method described above for compound 171B, using an appropriate amino acid in place of Boc-β-alanine.

**TABLE 12**

10

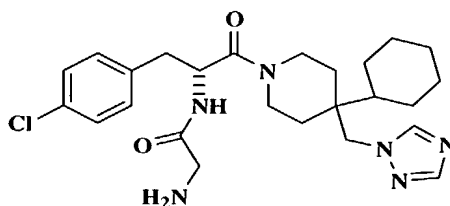
Ex.	R <sub>22</sub>	HPLC Retention Time (min)	MS Data (M + H) <sup>+</sup>
242		1.57 <sup>a</sup>	594
243		1.64 <sup>a</sup>	604
244	CF <sub>3</sub> -	1.66 <sup>a</sup>	596
245	CH <sub>3</sub> CH <sub>2</sub> -	1.50 <sup>a</sup>	556
246		1.50	639
247	(Me) <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> -	1.42	599
248	CH <sub>3</sub> OCH <sub>2</sub> -	1.48	572
249		1.64	607

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250		1.71	711
251		1.72	711

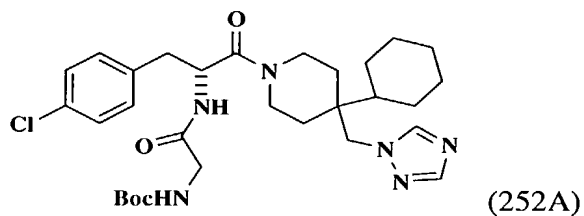
**EXAMPLE 252**

5            2-Amino-N-[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-acetamide



10

Step A:



15

To a solution of compound 171A (83 mg, 0.19 mmol) and N-Boc-glycine (86 mg, 0.49 mmol) in DMF (2 mL) was added EDCI (93 mg, 0.49 mmol), HOBT (66 mg, 0.49 mmol) and DIPEA (135  $\mu$ L, 0.78 mmol) at RT. The mixture was stirred at RT overnight

HA0768NP

and water (25 mL) was added. The aqueous layer was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with a solution of sodium bicarbonate (25 mL), water (25 mL), brine (25 mL) dried (Na<sub>2</sub>SO<sub>4</sub> anh.), filtered, and evaporated to afford the compound 252A which was used in the next step without purification.

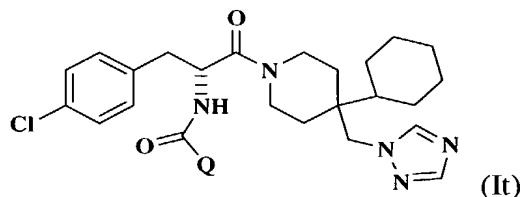
5

**Step B: Example 252**

To a solution of compound 252A (111 mg, 0.19 mmol) in DCM (5 mL) was  
 10 added TFA (2.5 mL) at RT. The mixture was stirred at RT for 15 min. and evaporated under reduced pressure. The residue was purified using preparative HPLC and after evaporation, the residue was purified by automated solid phase extraction and concentrated *in vacuo*. The product was dissolved in a 4 M HCl solution in dioxane and lyophilized to yield 70 mg of Example 252 as the hydrochloride salt (66 %). HPLC / MS  
 15 (L), ret. time = 1.41 min, purity 99 %, MS pos. *m/z* 487 (M+H)<sup>+</sup>; HPLC / MS (B), ret. time = 1.43 min, purity 97.8 %, MS pos. *m/z* 487 (M+H)<sup>+</sup>; MS (Finigan TSQ 7000, ESI) *m/z* 487 (M+H)<sup>+</sup>; IR (ν<sub>max</sub>, KBr) cm<sup>-1</sup> 3600-2854, 1683, 1625, 1456; <sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>) δ ppm (two rotamers; 1:1.2 ratio) 9.33 (1H, s), 9.26 (1H, s), 8.53 (1H, s), 8.46 (1H, s), 7.22-7.10 (4H, m), 4.99 (1H, t, J = 8.0 Hz), 4.32 (2H, s, major rotamer), 4.30  
 20 (2H, s, minor rotamer), 3.68-3.50 (2H, m), 3.40-3.34 (1H, m), 3.27-3.21 (1H, m), 2.92-2.75 (2H, m), 1.75-0.76 (15H, m).

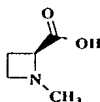
**EXAMPLES 253-54**

25 4-Amino-N-[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-butyramide



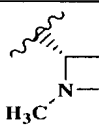
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The procedure described for the preparation of Example 252 was used to prepare compounds of formula (It), wherein Q has the values listed in Table 13, using N-Boc-3-

amino propionoic acid (Ex. 253) and  (Ex. 254), in place of N-Boc-glycine. Compounds were prepared as the hydrochloride salt. In compounds of formula (I),

5 Q=(CR<sub>11</sub>R<sub>12</sub>)<sub>y</sub>-(CH<sub>2</sub>)<sub>x</sub>-W.

TABLE 13

Ex.	Q	Compound Name	HPLC/MS (ret. time)	<sup>1</sup> H NMR
253	-(CH <sub>2</sub> ) <sub>3</sub> -NH <sub>2</sub>	4-Amino-N-[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-butyramide	1.42 <sup>L</sup> min; 1.43 <sup>b</sup> min;	(400 MHz, MeOH-d <sub>4</sub> ) δ ppm (two rotamers; 1:2 ratio) 9.30 (1H, s, major rotamer), 9.25 (1H, s, major rotamer), 9.23 (1H, s, minor rotamer), 9.20 (1H, s, minor rotamer), 8.51 (1H, s, major rotamer), 8.47 (1H, s, minor rotamer), 8.45 (1H, s, major rotamer), 8.41 (1H, s, minor rotamer), 7.29-7.09 (4H, m, major and minor rotamers), 4.91 (1H, t, J = 8.0 Hz), 4.31 (2H, s, major rotamer), 4.29 (2H, s, minor rotamer), 3.61-3.29 (2H, m), 3.40-3.35 (1H, m), 3.27-3.20 (1H, m), 3.05-2.74 (2H, m), 2.36 (1H, d, J = 4 Hz), 2.32 (1H, d, J = 8 Hz), 2.22 (2H, m), 1.95-0.82 (17H, m).
254		1-Methyl-azetidine-2-carboxylic acid[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	1.55 <sup>L</sup> min; 1.84 <sup>m</sup> min;	400 MHz, MeOH-d <sub>4</sub> ) δ ppm (two rotamers, 1:2) 9.30 (m, 1H, broad), 8.52 (m, 1H, broad), 7.33 (d, 2H, J = 8Hz, major rotamer), 7.28 (d, 2H, J = 8Hz, minor rotamer), 7.24 (d, 2H, J = 8Hz, major rotamer), 7.22 (d, 2H, J = 8Hz, minor rotamer), 5.10 (m,

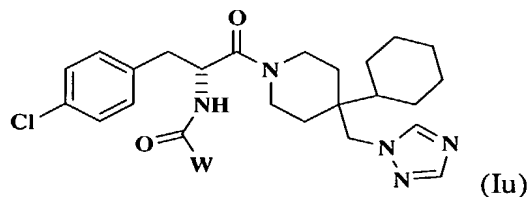


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				1H), 4.41 (s, 2H), 4.07-3.93 (m, 2H), 3.72-3.67 (m, 1H), 3.55-3.36 (m, 3H), 3.05-2.90 (m, 2H), 2.88 (s, 3H, major rotamer), 2.86 (s, 2H, minor rotamer), 2.77-2.65 (m, 1H), 2.40-2.19 (m, 1H), 1.80 (m, 3H), 1.68 (m, 3H), 1.54-0.90 (11H, m).
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**EXAMPLES 255-303**

5



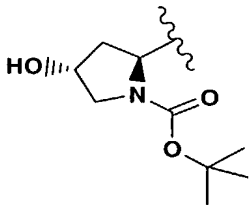
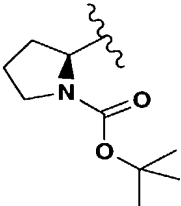
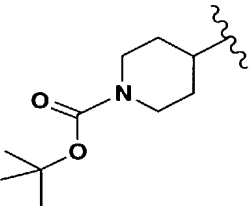
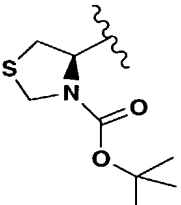
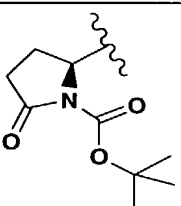
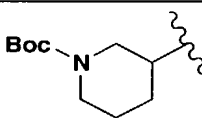
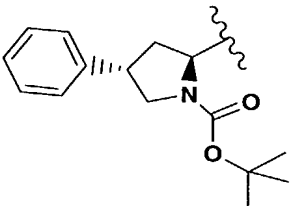
Compounds having the formula (Iu), wherein W has the values listed in Table 14, were prepared following the same or similar procedure described above for Example 171.

10

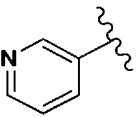
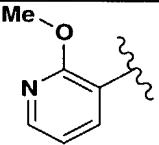
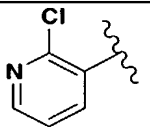
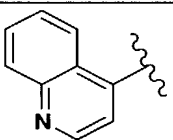
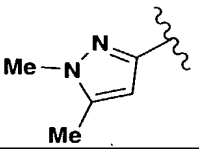
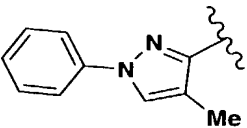
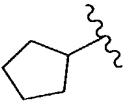
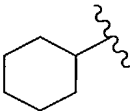
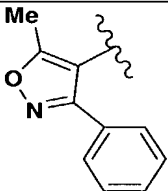
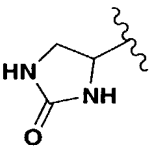
**TABLE 14**

Ex. No.	W	Purity (%)	HPLC ret. time (min)	Mass (M+H)
255		89.0%	3.9	627.43

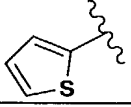
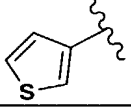
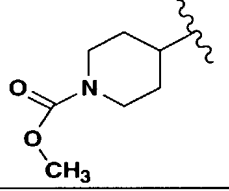
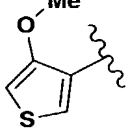
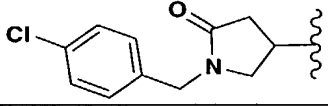
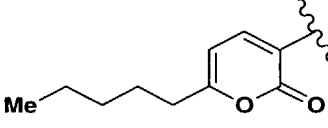
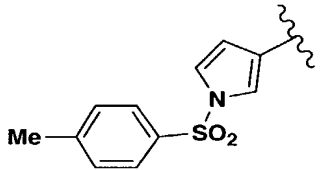
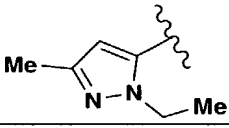
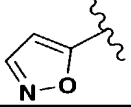
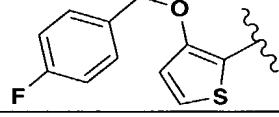
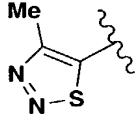
HA0768NP

256		90.0%	3.7	643.44
257		90.0%	4.0	627.45
258		86.0%	4.0	641.44
259		89.0%	4.0	645.4
260		90.0%	3.7	641.41
261		87.0%	4.1	641.47
262		90.0%	4.2	703.46

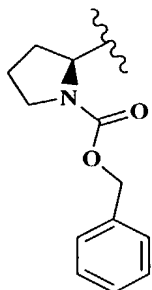
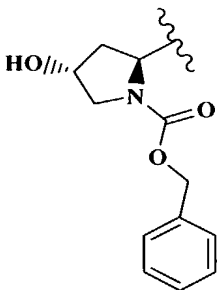
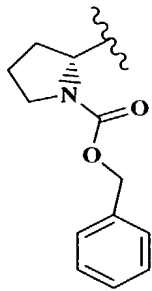
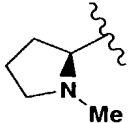
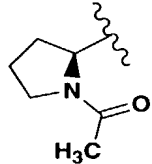
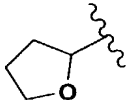
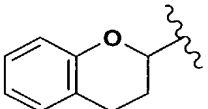
HA0768NP

263		91.0%	3.5	535.36
264		94.0%	4.0	565.36
265		93.0%	4.0	569.3
266		97.0%	3.6	585.38
267		96.0%	3.8	552.38
268		94.0%	3.9	614.42
269		91.0%	3.9	526.39
270		91.0%	4.0	540.41
271		92.0%	3.9	615.38
272		90.0%	3.4	542.36

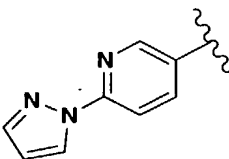
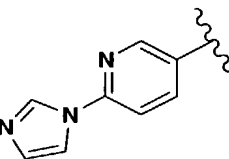
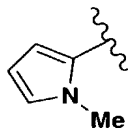
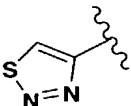
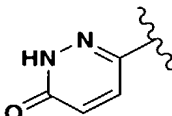
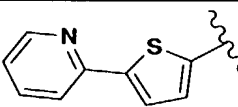
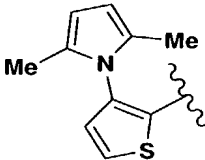
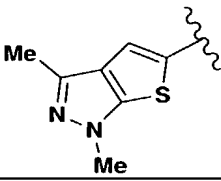
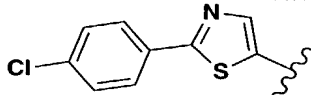
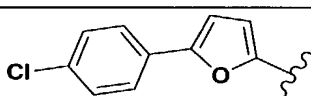
HA0768NP

273		92.0%	3.8	540.32
274		93.0%	3.8	540.32
275		91.0%	3.6	583.42
276		93.0%	3.9	570.33
277		86.0%	3.9	665.37
278		98.0%	4.2	622.42
279		94.0%	4.0	677.37
280		92.0%	3.9	566.4
281		92.0%	3.6	525.34
282		93.0%	4.1	664.34
283		91.0%	3.8	556.33

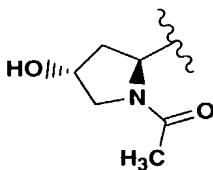
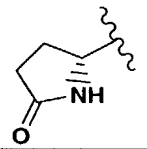
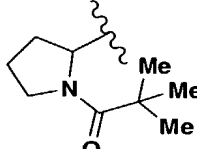
HA0768NP

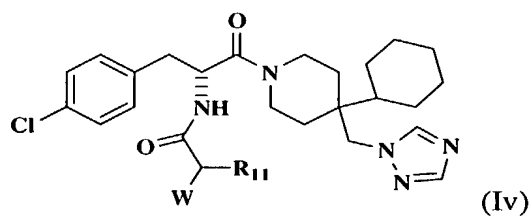
284		92.0%	4.0	661.43
285		92.0%	3.8	677.42
286		92.0%	4.0	661.43
287		83.0%	3.2	541.41
288		91.0%	3.6	569.39
289		88.0%	3.7	528.37
290		93.0%	4.1	590.39

HA0768NP

291		92.5%	4.0	601.37
292		83.5%	3.3	601.38
293		87.0%	.7	537.3
294		78.8%	3.7	542.28
295		89.8%	3.6	552.33
296		92.1%	3.9	617.34
297		90.6%	4.2	633.38
298		92.6%	3.9	608.36
299		93.2%	4.4	651.3
300		88.7%	4.3	634.33

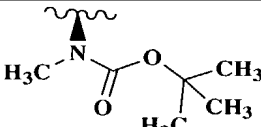
HA0768NP

301		92.8%	3.5	585.4
302		93.4%	3.5	541.36
303		93.8%	3.9	611.45

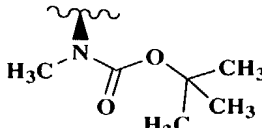
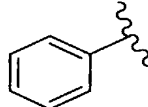
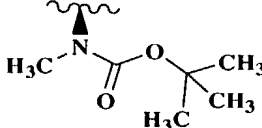
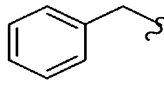
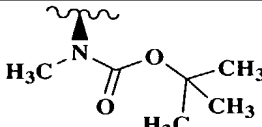
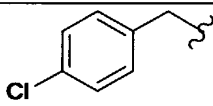
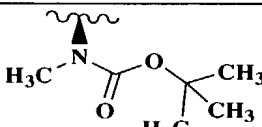
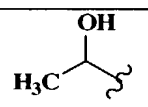
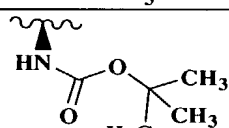
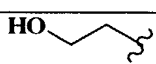
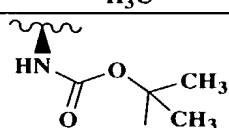
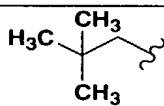
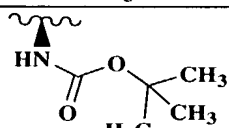
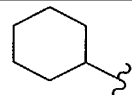

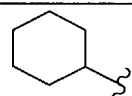

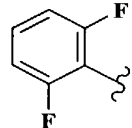

**EXAMPLES 304-319**

Compounds having the formula (Iv), wherein  $R_{11}$  and W have the values listed in Table 15, were prepared following the same or similar procedure described above for Example 171.

**TABLE 15**

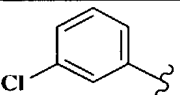

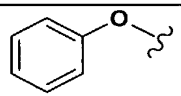
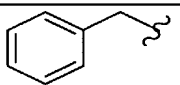
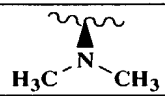
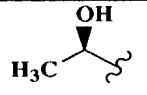
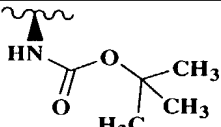
Ex. No.	$R_{11}$	W	Purity (%)	HPLC ret. time (min)	Mass (M+H)
304	$-\text{CH}_3$		92.0%	4.0	615.43

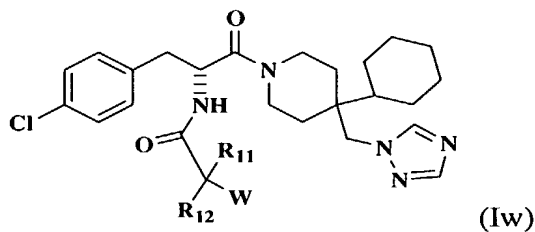
HA0768NP

305	-isoPr		88.0%	4.2	643.46
306			91.0%	4.2	677.45
307			89.0%	4.3	691.48
308			90.0%	4.4	725.43
309			90.0%	3.9	631.43
310			82.0%	3.8	631.43
311			90.0%	4.2	657.49
312			91.0%	4.1	570.41
313			92.0%	4.0	570.41
314		-OH	86.0%	3.7	600.36
315	-isoPr		91.0%	3.8	544.39



HA0768NP

316			91.0%	4.0	598.33
317	Et		92.0%	4.1	592.4
318			85.0%	3.5	605.43
319			91.4%	3.9	631.43



**EXAMPLES 320-322**

5

Compounds having the formula (Iw), wherein  $R_{11}$  and W have the values listed in Table 16, were prepared following the same or similar procedure described above for Example 171.

10

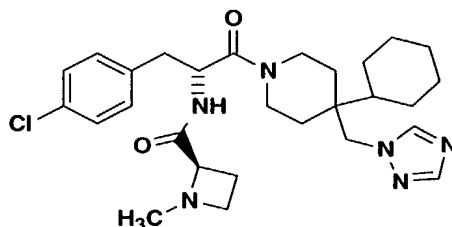
**TABLE 16**

Ex. No.	$R_{11}$	$R_{12}$	W	Purity (%)	HPLC ret. time (min)	Mass (M+H)
320	CH <sub>3</sub>	Et	-OH	62.0%	3.7	530.38
321	CH <sub>3</sub>	Ph		94.0%	4.0	578.38
322	CH <sub>3</sub>	Ph		93.0%	3.8	578.38

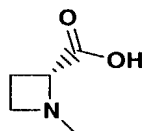
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**EXAMPLE 323**

**1-Methyl-azetidine-2-carboxylic acid[1-(4-chloro-benzyl)-2-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-2-oxo-ethyl]-amide**



To a solution of 2-Amino-3-(4-chloro-phenyl)-1-(4-cyclohexyl-4-[1,2,4]triazol-1-ylmethyl-piperidin-1-yl)-propan-1-one (Compound 171A) (79 mg, 0.18 mmol) and (R)-1-



methyl-azetidine-2-carboxylic acid **37** (32 mg, 0.28 mmol) in N,N-dimethylformamide (1.8 mL) was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (53 mg, 0.28 mmol), 1-hydroxybenzotriazole hydrate (37 mg, 0.28 mmol) and N,N-diisopropylethylamine (97  $\mu$ L, 0.56 mmol) at rt. The mixture was stirred 12 hours and then the solution was purified using preparative HPLC (Column: Column S-5 Phenyl 20 x 100 mm. Acetonitrile-0.05% TFA/water: 7 min. gradient from 10% AcCN to 90% AcCN at 220 nm. Flow rate: 20 mL/min.) and collected fractions were concentrated in vacuo. A second purification using preparative HPLC was done (Column: Column X-Terra C-8 21.2 x 100 mm. Acetonitrile- 5 mM NH<sub>4</sub>OAc/water: 7 min. gradient from 10% AcCN to 90% AcCN at 220 nm. Flow rate: 20 mL/min) and collected fractions were concentrated in vacuo. The hydrochloride salt was made using a solution of 4 M HCl in dioxane and the salt was lyophilized to yield 30 mg of Example 323. (31 %). HPLC / MS (Column: Xterra- C8 4.6 x 30 mm; Flow rate: 4 mL / min, Solvent system: 0-100% B in 2 min. Solvent A: 10% CH<sub>3</sub>CN - 90 %H<sub>2</sub>O – 5mM NH<sub>4</sub>OAc; Solvent B: 90% CH<sub>3</sub>CN - 10 %H<sub>2</sub>O – 5mM NH<sub>4</sub>OAc; UV: 220 nm; Micromass ZMD 2000, ESI): retention time 1.55

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min, purity 92.4 %, MS pos.  $m/z$  527 ( $M+H$ )<sup>+</sup> ; HPLC / MS (Column: YMC-Pack S5 Phenyl 4.6 x 50 mm; Flow rate: 3 mL / min, Solvent system: 0-100% B in 2 min. Solvent A: 10% CH<sub>3</sub>CN - 90 %H<sub>2</sub>O – 0.05 % TFA; Solvent B: 90% CH<sub>3</sub>CN - 10 %H<sub>2</sub>O – 0.05 % TFA; UV: 220 nm; Micromass ZMD 2000, ESI): retention time 1.83 min, purity 97.5 %,

5 MS pos.  $m/z$  527 ( $M+H$ )<sup>+</sup>; MS (Finigan TSQ 7000, ESI)  $m/z$  527 ( $M+H$ )<sup>+</sup>; HRMS *calculated for*: C<sub>28</sub>H<sub>39</sub>ClN<sub>6</sub>O<sub>2</sub> ( $M + H^+$ ) = 527.290128; *Found* = 527.291621; <sup>1</sup>H nmr (400 MHz, MeOH-d<sub>4</sub>)  $\delta$  ppm (two rotamers, 1:2) 9.60 (s, 1H, broad, minor rotamer), 9.57 (s, 1H, broad, major rotamer), 8.81 (dd, 1H, J = 4, 8 Hz), 8.74 (s, 1H, broad, minor rotamer), 8.69 (s, 1H, broad, major rotamer), 7.34-7.23 (m, 4H), 5.08 (m, 1H), 4.46 (s,

10 2H, major rotamer), 4.44 (s, 2H, minor rotamer), 4.16-3.97 (m, 2H), 3.77-3.60 (m, 2H), 3.52-3.46 (m, 1H), 3.40-3.35 (m, 1H), 2.99 (d, 1H, J = 8 Hz), 2.89 (s, 3H, major rotamer), 2.85 (s, 3H, minor rotamer), 2.80-2.71 (m, 1H), 2.54-2.45 (m, 1H), 1.80 (m, 3H), 1.68 (m, 3H), 1.54-0.90 (m, 11H).